

[CASE REPORT]

Metachronous Esophageal Ulcers after Immune-mediated Colitis Due to Immune Checkpoint Inhibitor Therapy: A Case Report and Literature Review

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Abstract:

Although cases of gastrointestinal toxicity of pembrolizumab have been reported, cases of acute immune-mediated colitis accompanied with metachronous esophageal disorders (esophagitis and ulcer) are rare. We herein report a case of acute colitis and metachronous esophageal ulcers due to an immune-related adverse event following concomitant pembrolizumab chemotherapy for lung adenocarcinoma. To our knowledge, there have so far been no reports of cases in which both acute immune-mediated colitis and metachronous esophageal ulcers developed. We therefore report the details of this case along with a review of the pertinent literature.

Key words: ICI, immune-mediated colitis, metachronous esophageal ulcer, pembrolizumab, steroid administration

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Introduction

The recent introduction of immune checkpoint inhibitors (ICIs) has increased the frequency of use of these drugs in daily clinical practice. ICIs are known to cause immune-related adverse events (irAEs) that occur via a mechanism that differs from that of adverse events associated with conventional anti-cancer drugs. As the clinical use of ICIs increases, a concomitant increase in gastrointestinal mucosal disorders is expected. We herein report a case in which acute immune-mediated colitis and metachronous esophageal ulcers developed during the course of chemotherapy with pembrolizumab, along with a review of the pertinent literature.

Case Report

A 60-year-old man with abdominal pain, diarrhea, and bloody stool was referred to our department. His medical history was as follows: appendicitis (at the age of 13 years of age), cerebral infarction (at the age of 47 years), and bilateral hip arthroplasty (at the age of 54 years). His life history was as follows: drinking history - ethanol 72 g/d (since the age of 20 years); and smoking history - 60 cigarettes/dx 40 years (20-59 years).

The patient underwent an enema X-ray examination during a health checkup in April 2019. The examination indicated a mass lesion in the sigmoid colon. Colonoscopy (CS) performed by a local doctor thereafter revealed a steeply rising tumor in the sigmoid colon. The tumor margin was composed of a normal mucosa, and only the central recess

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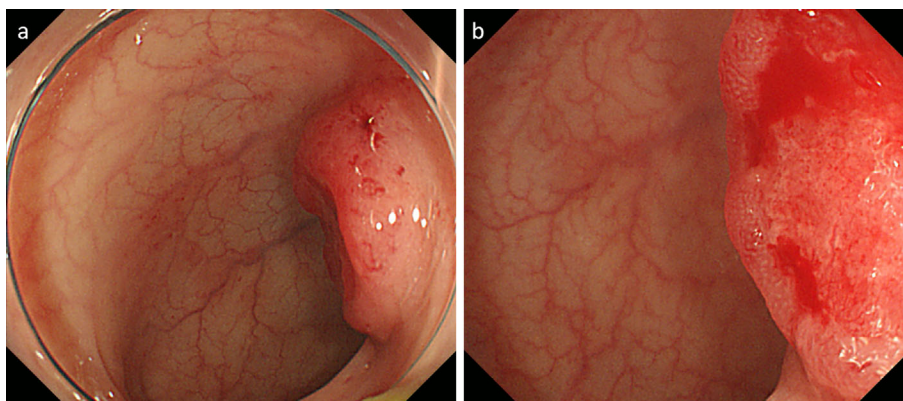


Figure 1. Colonoscopic findings by a former doctor. The examination indicated a mass lesion revealed a steeply rising in the sigmoid colon. The tumor margin was composed of normal mucosa, and only the central recess area was reddish and accompanied by vascular atypia.

area was reddish and accompanied by vascular atypia (Fig. 1).

A biopsy revealed a poorly differentiated adenocarcinoma. Subsequent systemic examinations revealed a mass lesion in the upper lobe of the right lung and extensive right pleural effusion. Metastatic lesions were suspected based on the macroscopic morphology of the sigmoid colon tumor, which was atypical as the primary lesion.

The patient was diagnosed with sigmoid colon metastasis of the primary lung cancer, carcinomatous pleurisy, and lymph node metastasis (hilar, parabronchi, tracheal bifurcation, para-aorta, para-esophagus, and supraclavicular fossa), and thus was admitted to the division of respiratory of our hospital. The patient was treated with concomitant carboplatin, pemetrexed, and pembrolizumab chemotherapy for right hilar lung adenocarcinoma (cTXN3M1c, cStage IVb) from June 2019. He patient developed febrile neutropenia on d 13, and antibacterial drug (tazobactam/piperacillin) administration was started.

There were no particular issues with defecation habits both prior to and during the course of treatment. However, the patient experienced spontaneous abdominal pain followed by bloody diarrheal stool and bloody stool over 20 times on d 14. Therefore, on d 15, he was referred to our department for a thorough examination. The laboratory data were as follows: Grade 3 neutropenia (Common Terminology Criteria for Adverse Events: CTCAE ver. 4.0) with a white blood cell count of $1,900/\text{mm}^3$ and neutrophil count of $889/\text{mm}^3$; C-reactive protein level of 2.78 mg/dL; and mild anemia with a hemoglobin level of 12.1 g/dL. Transaminases were outlier [aspartate aminotransferase 46 U/L (normal range: 13-30 U/L) and alanine aminotransferase 92 U/L (normal range: 10-42 U/L)], and no renal dysfunction or thyroid dysfunction was observed [blood urea nitrogen 11.7 mg/dL (normal range: 8-20 mg/dL), serum creatinine 0.95 mg/dL (normal range: 0.65-1.07 mg/dL), thyroid-stimulating hormone 1.27 $\mu\text{IU}/\text{mL}$ (normal range: 0.35-4.94 $\mu\text{IU}/\text{mL}$), free triiodothyronine 2.6 pg/mL (normal range: 1.88-3.18 pg/mL) and free tetraiodothyronine 0.78 ng/dL

(normal range: 0.7-1.48 ng/dL)].

A CS was conducted for a careful examination owing to the bloody diarrheal stools and bloody stools. The CS findings (Fig. 2) included circumferential edematous changes, dark-purple rough mucosa, mucous adhesion, and erosion in the intestinal tract on the oral side of the sigmoid colon 30 cm from the anal margin. The patient experienced severe pain during CS; therefore, the observations were limited to the lower part of the descending colon, and the edematous mucosa of the sigmoid colon was biopsied. The mass lesion in the sigmoid colon, which was observed by a previous doctor, could not be confirmed. The entire colon could not be observed with the CS; therefore, contrast-enhanced computed tomography (CT) was performed to confirm the lesion and determine its extent.

Contrast-enhanced CT (Fig. 3) revealed severe, continuous circumferential wall thickening from the ascending colon to the sigmoid colon. Submucosal edema was particularly significant. Furthermore, increased adipose tissue concentration around the intestinal tract and mild ascites retention in the pelvic cavity were observed.

It was difficult to distinguish between carboplatin-induced or pembrolizumab-induced colitis and ischemic colitis based on the patient's symptoms and CS findings. CT revealed that the lesion had spread over the entire large intestine, which was atypical for ischemic colitis. Specific bacteria were not identified in stool cultures collected during the colonoscopy procedure; therefore, infectious enteritis was deemed to be unlikely.

Thus, a diagnosis of Grade 3 immune-mediated colitis was made based on CTCAE ver. 4.0. The administration of anticancer drugs was suspended and intravenous steroid (prednisolone; PSL) injection therapy (60 mg/d) started. Treatment also involved fasting and fluid replacement management. Abdominal pain, bloody diarrheal stools, and bloody stools improved 5 days after the start of treatment (d 19). The results of the histopathological examination of the edematous mucosa of the sigmoid colon are shown in Fig. 4.

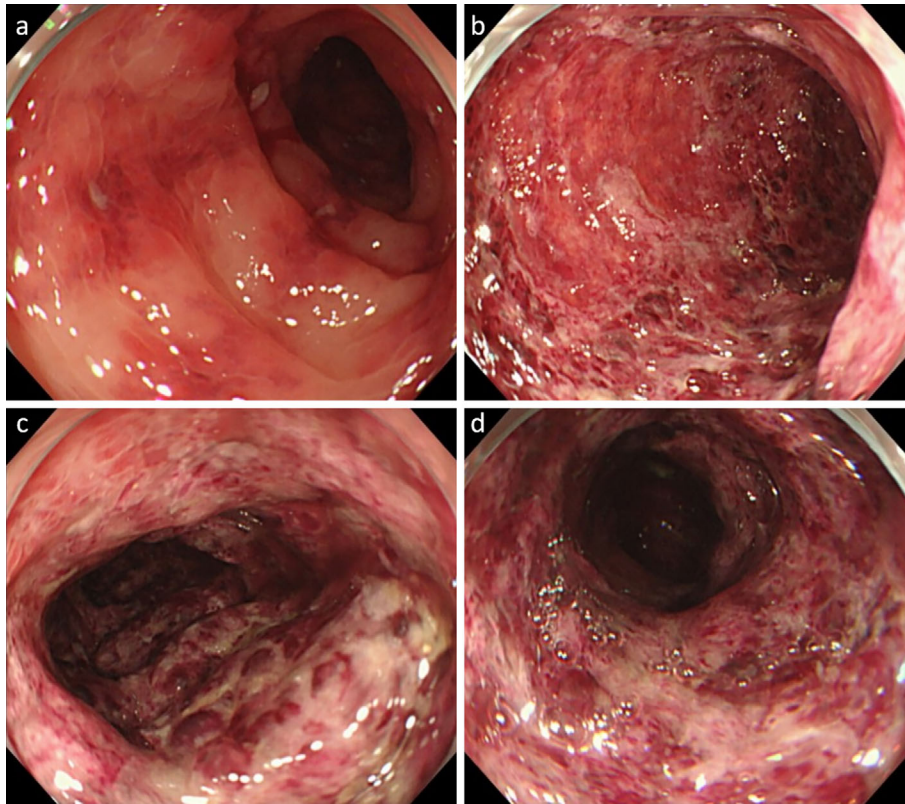


Figure 2. Colonoscopic findings. The examination indicated circumferential edematous changes, dark-purple rough mucosa, mucous adhesion, and erosion in the intestinal tract on the oral side of the sigmoid colon 30 cm from the anal margin.

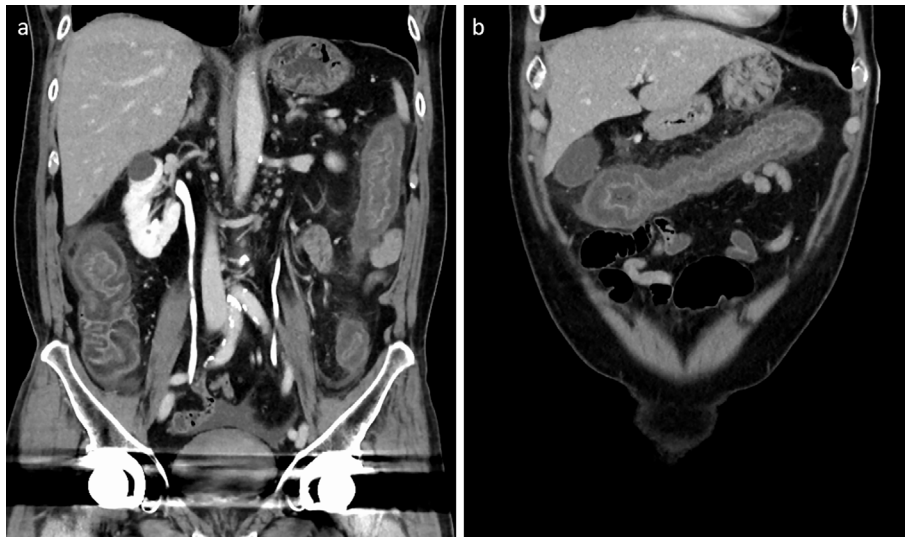


Figure 3. Abdominal contrast-enhanced computed tomographic findings. Severe, continuous circumferential wall thickening was observed from the ascending colon to the sigmoid colon. Submucosal edema was particularly significant. Furthermore, increased adipose tissue density concentration around the intestinal tract and mild ascites retention in the pelvic cavity were observed.

Further examination revealed surface layer erosion and hemorrhaging, and mild lymphocyte infiltration in the lamina propria. Only a few apoptosis-like changes were observed; there were no crypt abscesses, and neutrophil inflammation was mild (Fig. 4a). Immunohistochemical staining showed no bias in CD4- and CD8-positive T cells

(Fig. 4b).

Repeat CS performed 2 weeks after the start of PSL treatment showed improved mucosal findings of the sigmoid colon (16 days) (Fig. 5). No clearly abnormal findings were noted during the observation of the entire colon. Thereafter, the PSL administration was gradually reduced, and abdomi-

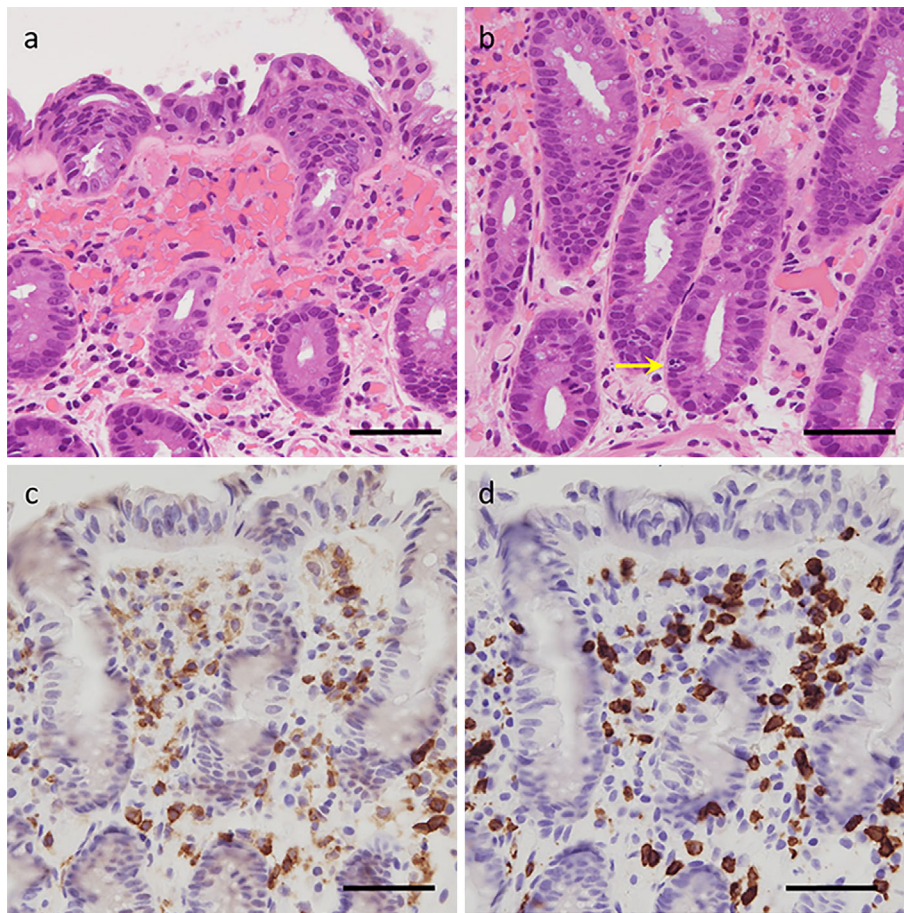


Figure 4. Histopathological findings in the sigmoid colon. The examination revealed surface layer erosion and hemorrhaging, and mild lymphocyte infiltration in the lamina propria (arrow). Only a few apoptosis-like changes were observed; there were no crypt abscesses, and neutrophil inflammation was mild (a). Immunohistochemical staining showed no bias in CD4- and CD8-positive T cells (b) (the scale bar shows 50 μ m).

nal symptoms did not recur. Intravenous PSL administration (60 mg/d) was continued for 1 week, after which it was switched to oral administration (40 mg/d). The dose was gradually reduced by 10 mg/week until a dose of 10 mg/d was reached. Thereafter, a dose of 10 mg/d was administered for 4 weeks, followed by 5 mg/d for 2 weeks, and 4 mg/d for 4 weeks. Then, the dose was reduced to 2 mg/d and 1 mg/d in 1 week, with administration concluding on d 120. Oral rabeprazole sodium (5 mg/d) was concomitantly administered during oral PSL administration.

The progress was favorable; however, epigastric pain developed on d 109 of pembrolizumab administration (d 84 of PSL treatment, oral administration at 4 mg/d), and the patient was once again referred to our department. Laboratory data showed the number of white blood cells to be elevated, but the patient had normal C-reactive protein levels and no hepato-renal dysfunction at the time of re-examination. Esophagogastroduodenoscopy (EGD) was conducted with the aim of carrying out a careful examination.

EGD (Fig. 6): Mottled white patches were mainly noted in the soft palate of the oropharynx, indicative of oral candidiasis. Shallow and extensive map-like ulcers were ob-

served extending from the upper esophagus 17 cm from the incisor to the gastric junction of the esophagus. The ulcer margin was reddish, and regenerated epithelium was observed. A biopsy was performed from the margin of the esophageal ulcer at the time of the EGD. However, there was no epithelial component, and immunohistological analyses could not be conducted.

PSL was administered for the management of colitis. Esophageal lesions developed despite the concomitant use of 5 mg/d rabeprazole sodium. The lesion was widespread, and its extent was relatively uniform according to its esophageal site. Therefore, this was considered to be atypical for reflux esophagitis. An EGD was conducted in May 2019 before chemotherapy treatments began, which detected a hiatal hernia, but reflux esophagitis was not observed. Moreover, atrophic gastritis was also not shown in the stomach. The patient's history with *Helicobacter pylori* (*H. pylori*) is unknown, particularly as *H. pylori* antibody levels in serum samples were absent (<3 U/mL; normal range <3 U/mL). Therefore, we diagnosed the esophagitis as being due to an irAE. Rabeprazole was switched to 20 mg/d vonoprazan fumarate, and the oral administration of 90 mL/d sodium algi-

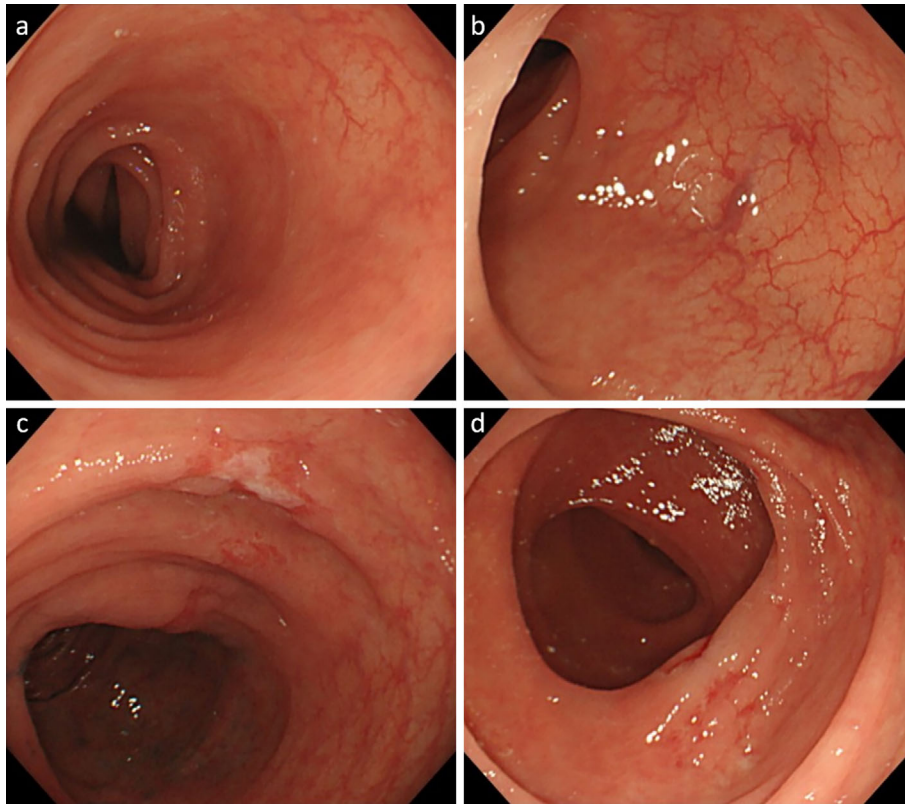


Figure 5. Colonoscopic findings on 15 days of steroid treatment. Follow-up colonoscopy showed improved mucosal findings of the sigmoid colon.

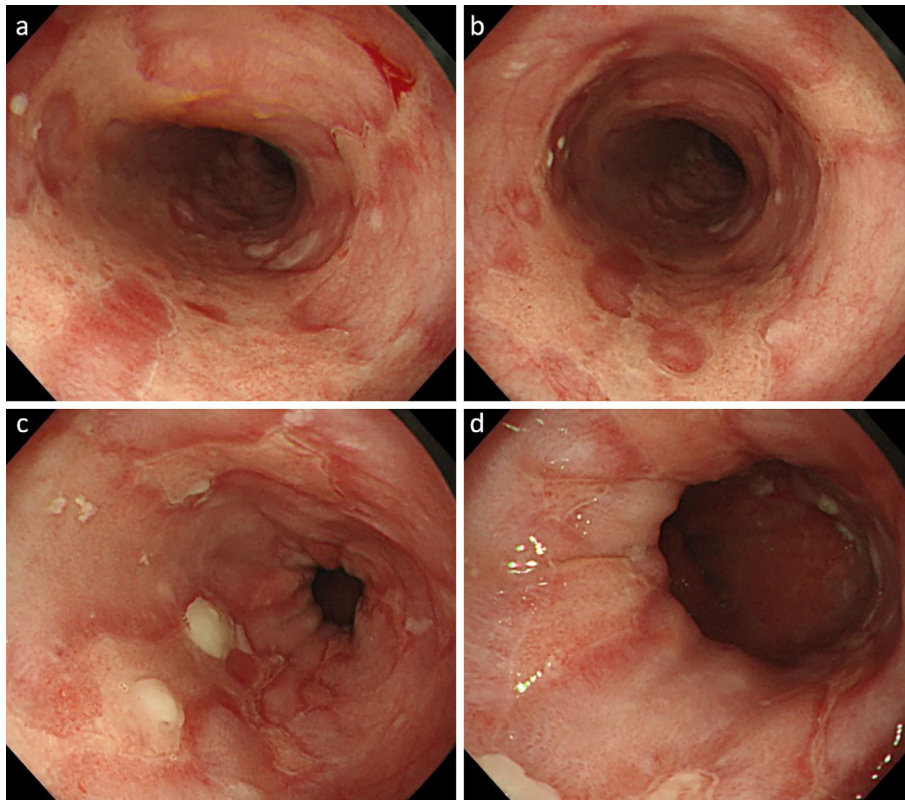


Figure 6. Esophagogastroduodenoscopic findings on day 100 of steroid treatment. Shallow and extensive map-like ulcers were observed extending from the upper esophagus 17 cm from the incisor to the gastric junction of the esophagus. The ulcer margin was reddish, and a regenerated epithelium was observed.

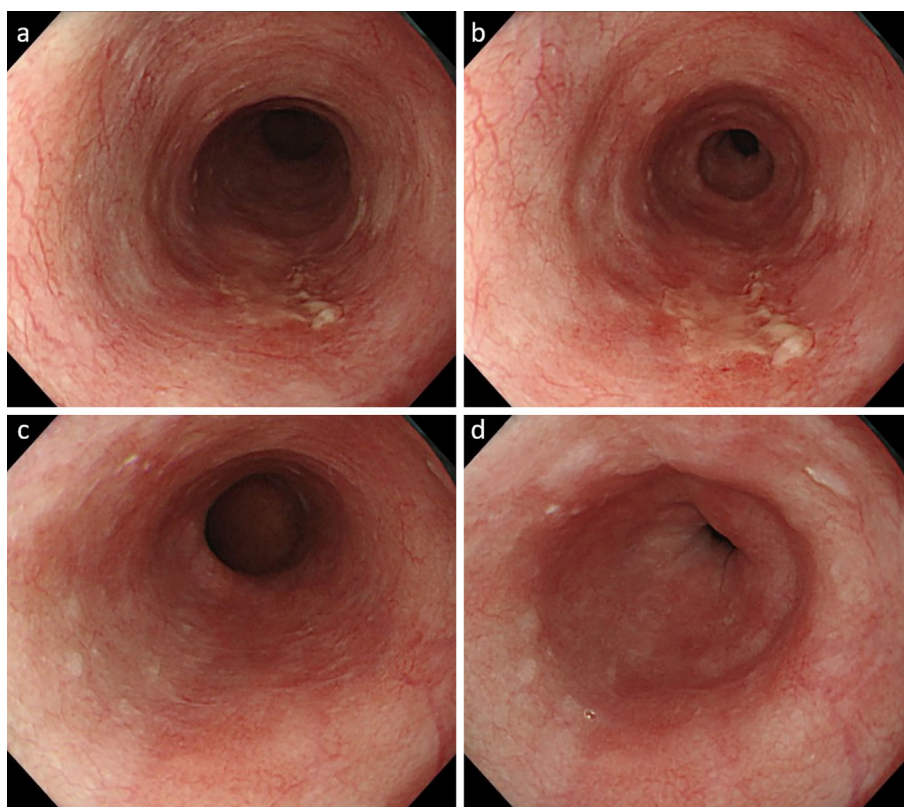


Figure 7. Esophagogastroduodenoscopic findings on day 107 of steroid treatment. Follow-up esophagogastric duodenoscopy showed healing of the esophageal ulcer.

nate was also started.

An EGD conducted 1 week later showed that these treatments had a healing effect on the esophageal ulcer (Fig. 7), and oral candidiasis resolved. Although PCR tests for cytomegalovirus (CMV) and herpesvirus (HSV) were not performed, there were no characteristics of CMV/HSV, such as intranuclear inclusion bodies, in the biopsied tissues. In addition, the esophagitis improved without any antiviral treatment, suggesting that an unusual viral infection caused esophagitis in the patient. Moreover, there have been no reports of drug-induced esophagitis with PSL and anticancer drugs, except for pembrolizumab.

The oral administration of PSL was stopped on d 118. There was no subsequent recurrence of gastrointestinal symptoms. Concomitant carboplatin and pemetrexed chemotherapy (excluding pembrolizumab) was changed as the second-line therapy for the lung cancer. A modified course of treatment was started in October 2019 (d 108). Neither the colitis nor the esophagitis became exacerbated during the second course of chemotherapy treatment with the same dose of the first course that lacked except pembrolizumab. Therefore, immune-mediated colitis was diagnosed during the first course of chemotherapy. The patient's general condition worsened due to thrombocytopenia and liver dysfunction in December 2019, and the patient died due to the primary disease in January 2020.

Discussion

We herein report a case of acute colitis and metachronous esophageal ulcers due to an irAE following concomitant pembrolizumab chemotherapy for lung adenocarcinoma. With regard to ICIs in Japan, anti-CTLA-4 antibody and anti-PD-1/PD-L1 antibody preparations for use against malignant melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, and head and neck cancer are covered by insurance. Both types of preparations exhibit antitumor effects by activating an immune response to tumor cells. However, the use of these preparations is also known to lead to various irAEs including skin disorders, gastrointestinal toxicity (enteritis and diarrhea), autoimmune hepatitis, endocrine disorders (hypophysitis and thyroiditis), interstitial pneumonia, and myasthenia gravis (1).

Gastrointestinal toxicity is the second most common adverse event (11.6%) associated with the use of these preparations, behind skin disorders (15%) (2). Shivaji et al. (3) reported treatment-related diarrhea in 6.6-12.5%, 1.1-1.8%, and 0.4-2.2% among those who used anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibody preparations, respectively. The corresponding percentages of those with serious diarrheal complications of Grade 3 or 4 were 5.5-11.4%, 1-1.7%, and 0.1-1.1%.

The concomitant use of anti-PD-1 antibody and anti-CTLA-4 antibody preparation therapy against malignant

melanoma and renal cell carcinoma is also currently covered by national insurance. However, the risk of immune-mediated colitis increases with this type of concomitant therapy, and it has been reported that 13.6% of patients in whom these treatments were used developed enteritis complications (4). Furthermore, severe complications (CTCAE Grade 3 or higher) were reported in 9.4% of cases (3). Compared to monotherapy, the concomitant use of these two preparations increases the frequency of diarrhea and enteritis; therefore, more careful examinations are necessary.

The risk factors for immune-mediated colitis include a history of inflammatory bowel disease, the use of non-steroidal anti-inflammatory drugs and medical narcotics, concomitant use of anti-PD-1 and anti-CTLA-4 antibody preparation therapy, malignant melanoma (lung cancer and renal cell carcinoma), and an increase in members from Firmicutes phylum among intestinal flora (5).

Our patient did not have a history of using non-steroidal anti-inflammatory drugs and narcotics; subsequently, the ICI used for lung adenocarcinoma was an anti-PD-1 antibody preparation. Therefore, the patient was not at a clear risk of immune-mediated colitis. However, there have been no reports on the development of immune-mediated colitis according to individual risk factors, and large-scale reports based on further case accumulation are therefore needed.

Nishida et al. (6) reported that the onset of gastrointestinal toxicity (diarrhea/colitis) depended on the type of drug used. It has been reported that the onset of symptoms often occurred 6-7 weeks after the initial administration in the case of anti-CTLA-4 antibody preparations, whereas this was delayed in the case of anti-PD-1/PD-L1 antibody preparations. It has also been reported that the onset of symptoms often occurs within 4 months of starting treatment (7). Our patient developed immune-mediated colitis at an early stage of approximately 2 weeks after starting treatment. This finding differs from those reported previously; however, it should be noted that immune-mediated colitis can develop at an early stage after starting drug administration.

Redness, the disappearance of the vascular structure, erosion, ulcers, and granular mucosa have been reported as characteristic CS findings of immune-mediated colitis. Of these, granular mucosa with lost vascular structure has often been reported as an ulcerative colitis-like mucosal lesion, which is considered to be a characteristic finding of immune-mediated colitis (8). Reports have not indicated any clear differences in the distribution or findings of lesions between anti-CTLA-4 antibody and anti-PD-1/PD-L1 antibody preparations (2, 9, 10, 11). The CS findings in our patient were consistent with those of ischemic colitis.

The histopathological characteristics of immune-mediated colitis include infiltration of inflammatory cells in the mucosa, crypt abscesses, cryptitis, and apoptosis (8). Predominance of CD4-positive T cells has been reported in patients with colitis due to anti-CTLA-4 antibody preparations, while that of CD8-positive T cells was observed in patients with colitis due to anti-PD-1 antibody preparations (12). Mean-

while, non-specific findings such as an increase in the number of cells in the lamina propria (monocyte predominance) and migration of neutrophils into the mucosa have been observed, and it has been reported that there were no clear differences in the histopathology between these preparations (13).

In our case, the histopathological images showed erosion and bleeding on the surface of the colon mucosa, but crypt abscesses or inflammation induced via neutrophils were not conspicuous. Immunohistochemistry showed no differences between CD4- and CD8-positive T cells. Nevertheless, we observed unusual histopathological characteristics from immune-mediated colitis derived from anti-PD-1 antibody preparations. Throughout the course of colitis and from microscopic examination, infectious enterocolitis (e.g., CMV, *Clostridioides difficile*, or parasite infection) were unlikely. Moreover, ischemic colitis was also unlikely as the CT images showed extensive colitis, resulting in the diagnosis of immune-mediated colitis. Fortunately, the diagnostic treatment for immune-mediated colitis, PSL, was effective.

Interestingly, our patient experienced epigastric pain approximately 15 weeks after the onset of immune-mediated colitis, and this was accompanied by metachronous esophageal ulcers induced via ICI therapy. A PubMed search from January 2015 to June 2020 with the keywords “pembrolizumab” and “esophagitis” showed five case reports (including our own) on esophagitis due to pembrolizumab (Table) (14-17). All cases other than our own were of esophagitis, and there were complications of oral mucosal damage in two of the four cases, of which one showed complications of uveal and penile mucosal damage. Furthermore, one of the four cases showed gastritis, duodenal inflammation, and enteritis as well as symptoms such as fever and abdominal pain. With regard to treatment, one out of the four patients was in remission due to drug discontinuation, while the other three received PSL treatment. One of these three patients received infliximab-based treatment. Furthermore, regarding the onset time, our patient had an atypical onset after colitis treatment, whereas, in the other four cases, the onset time was the same as the treatment period.

Our patient did not experience epigastric pain for approximately 2 months following the onset of immune-mediated colitis. Furthermore, CT scans performed during this time did not indicate clear thickening or edematous findings in the esophageal wall. The onset time of esophageal ulcers was not clear; however, at the very least, the patient did not complain of epigastric pain during the onset of colitis. The possibility that symptoms caused by esophageal ulcers were subclinical due to therapeutic intervention with PSL or concomitant rabeprazole sodium thus cannot be ruled out.

In previous studies, the onset of irAE esophageal ulcer occurred over a period of 2 or more months (14-17). Nivolumab, that is, the anti-PD-1/PD-L1 antibody, has also been reported to cause colitis and esophagitis due to an irAE, which developed 6 months after using nivolumab for Hodgkin's lymphoma (18). The incidence of irAE esopha-

Table. Summary of Immune-related Adverse Events of Esophageal Lesions Caused by Pembrolizumab.

Reference	Underlying disease	Esophageal lesion	Dose of Pembrolizumab	Onset time	Treatment of esophageal lesion	Other adverse events	Time of onset of adverse events
14	Metastatic laryngeal cancer	Esophagitis	200 mg/3 w	After 14 course (Day 294)	Drug discontinuation (change), mPSL 2 mg/kg/day	Oral mucosal disorder	Simultaneity
15	Recurrent thymoma	Esophagitis	50 mg/3 w	After 4 course (Day 84)	Drug discontinuation (change), PSL, IFX, Plasmapheresis, Immunoglobulin administration	Ocular, penile, and oral mucosal disorder, Dermatitis	Simultaneity
16	Metastatic non-small cell lung cancer	Esophagitis	200 mg/3 w	After 7 course (Day 140)	Drug discontinuation (change), PSL 1 mg/kg/day, PPI intravenous administration	Gastric, duodenal, colonic inflammation	Simultaneity
17	Metastatic non-small cell lung cancer	Esophagitis	200 mg/3 w	After 3 course (Day 63)	Drug discontinuation (change), P-CAB oral administration	None	None
Our case	Metastatic non-small cell lung cancer	Esophageal ulcers	200 mg/3 w	After 1 course (Day 110)	Drug discontinuation (change), PSL 1 mg/day, PPI oral administration	Colonic inflammation	Asynchronous

PSL: prednisolone, mPSL: methylprednisolone, IFX: infliximab, PPI: proton pump inhibitor, P-CAB: potassium-competitive acid blocker

geal ulcers was low; however, there was the possibility of a delayed onset, as was noted in our patient. Therefore, long-term, careful follow-up observations including symptom evaluations are required.

Conclusion

We herein described a case of acute colitis and metachronous esophageal ulcers as irAEs due to ICI therapy for lung cancer. Thus far, there have been no reports on the complications of both illnesses, and hence, the findings of our case are deemed to be valuable.

The patient gave his informed consent for us to publish these findings.

The authors state that they have no Conflict of Interest (COI).

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