A case of nivolumab-associated colitis, which relapsed after mucosal healing and was then successfully treated with mesalazine

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ABSTRACT
Currently, the number of patients treated with immune-checkpoint inhibitor involving nivolumab is increasing. Nevertheless, it causes various immune-related adverse events (irAEs). Here, we report the case of a patient who underwent long-term follow-up after suffering from nivolumab-associated colitis. The patient was a 57-year-old man who underwent resection of a bladder tumor. Following surgery, lymph node metastasis was detected, and he was treated by nivolumab. Two months after treatment with nivolumab, the patient complained of bloody diarrhea. Colonoscopy revealed pancolitis with erosions, loss of vascular pattern and erythema. Pathological findings indicated a disease state of pan-ulcerative colitis. As an irAE by nivolumab, the patient was started with 30 mg of prednisolone. Prednisolone treatment successfully induced clinical remission and mucosal healing. Nevertheless, eight months after stopping the steroid treatment, the colitis relapsed with diarrhea following elevation of fecal immunochemical test (FIT) and fecal calprotectin (CPT). The relapsed colitis was treated by mesalazine, and then diarrhea was improved. Nivolumab-associated colitis relapsed following mucosal healing suggesting that it is necessary to consider maintenance therapy as well as remission induction for long-term survivor. The present case also demonstrates that the FIT and CPT would be effective biomarker to assess the disease activity of nivolumab-associated colitis.

1. Introduction
Nivolumab is an anti-cancer drug that functions via immune-checkpoint inhibition [1,2], and its frequency of use has increased [3]. However, nivolumab causes several immune-related adverse events (irAEs) and particularly results in intestinal inflammation resembling ulcerative colitis [4–6]. The first line of recommended treatment for this condition is steroid therapy; however, anti-tumor necrosis factor (TNF)-alpha agents are usually administered in intractable cases [7,8]. Despite the existence of recommended treatment strategies, it remains unclear whether maintenance treatment is necessary or not after achievement of remission. We present a case involving the relapse of nivolumab-associated intestinal inflammation after steroid-free mucosal healing.

2. Case
A 57-year-old man who had been diagnosed with bladder cancer, two years back was admitted to the Department of Urology in our hospital and underwent radical cystectomy, ileal neobladder plasty and lymphadenectomy. Metastasis to the right external iliac and internal iliac lymph node was detected, and adjuvant chemotherapy consisting of oral tegafur-uracil (UFT) was initiated. Six months later, a CT scan revealed that the size of the lymph node metastasis had increased. The patient underwent secondary chemotherapy with gemcitabine and cisplatin. However, CT findings indicated that the disease had progressed; the lymph node metastasis had extended to an abdominal para-aortic lymph node and the inferior vena cava. The chemotherapy was discontinued at the request of the patient and best supportive care was provided. After being thoroughly briefed by a urologist, the patient consented to treatment with nivolumab. The patient started receiving 3 mg/kg Opdivo® (nivolumab) every two weeks. Following six cycles of nivolumab administration, CT revealed that the lymph node metastasis had reduced in size by 60%. However, two months...
After start of nivolumab treatment, the patient complained of bloody diarrhea over 10 times in a day. Despite receiving an anti-flatulent, the patient continued to suffer from bloody diarrhea. Therefore, the nivolumab treatment was discontinued and the patient visited our department.

On physical finding, the patient had weight loss as well as bloody stool. However, he complained no abdominal pain and his body temperature or blood pressure was within normal range. A blood test revealed mild anemia (hemoglobin 12.1 g/dL) and hypoalbuminemia (2.7 g/dL), and his CRP was slightly elevated (0.329 mg/dL). Especially, the fecal immunochemical test (FIT) value was markedly high (987 ng/mL). The patient was also examined for infections, and there were no pathogenic bacteria on fecal culture; furthermore, tests for *Clostridium difficile* toxin and cytomegalovirus antigen were negative. He did not have any other irAEs except colitis, e.g. skin rash, hypophysitis, thyroid dysfunction, liver damage, type 1 diabetes and so on.

Colonoscopy revealed friability, erosion, complete loss of vascular pattern, significant erythema, and mild mucosal hemorrhage with mucous exudate from the rectum to the cecum (Figure 1). These findings are typical signs of moderate pan-ulcerative colitis (UC). Biopsy revealed diffuse and severe mononuclear cell infiltration, distal paneth cell metaplasia, and basal plasmacytosis, suggesting a state resembling UC. However, distortion and atrophy of the intestinal crypts were mild in comparison to that observed in typical UC (Figure 2). Esophagastroduodenoscopy revealed no abnormalities. A CT scan revealed thickening of the bowl wall from the rectum to the cecum (Figure 3). No inflammation was detected in the small intestine.

The cause of colitis was considered to be nivolumab-associated irAEs. Therefore, administration of 30 mg of prednisolone was initiated. After two weeks of prednisolone administration, the patient’s symptoms improved rapidly. Eight months later, colonoscopy revealed endoscopic and histological remission, a state that is also called mucosal healing (Figure 4), and prednisolone was discontinued. Unexpectedly, six months after steroid discontinuation, the patient’s FIT values began to increase. At 14 months after nivolumab discontinuation, the patient did not have any abdominal symptoms, formed stool once a day, and had a FIT value of 155 ng/mL. However, during the next visit at 15 months after nivolumab discontinuation, he complained of soft stool once or twice a day, and his FIT and fecal calprotectin (CPT) values were 6 ng/mL and 52.9 mg/kg, respectively. The third colonoscopy, performed 16 months after nivolumab discontinuation, revealed colitis relapse, and the patient experienced soft or watery diarrhea three or four times a day; moreover, his FIT (961 ng/mL) and CPT values (633.0 mg/kg) were observed to have increased substantially. Unlike in the case of typical left-sided UC, the inflammation at this relapse was observed in the recto-sigmoid colon, segmental
descending colon and the peri-appendiceal patch (Figure 5). A few apoptotic epithelial cells were observed in a biopsy specimen from the rectum (Figure 6). The relapsed colitis was treated with mesalazine, 4800 mg per day. After the treatment with mesalazine, the symptoms of diarrhea promptly improved with a decrease in both FIT (12 ng/mL) and CPT (102.0 mg/kg) values. Before and after the relapse phase, the changes in the CPT values coincided with the FIT values. Treatment with mesalazine as maintenance therapy was continued (Figure 7).

After nivolumab discontinuation, the patient was not administered any anti-cancer drugs. Fortunately, his cancer did not progress while he had irAE-associated colitis. Subsequently, 20 months after nivolumab discontinuation, while his irAE colitis disappeared, para-aortic and para-inferior vena cava lymph-node enlargement due to metastasis was observed.

3. Discussion

This is the first report to show that nivolumab-associated colitis has a possibility of relapsing even if clinical, endoscopic and histological remission of mucosal inflammation is achieved.

Nivolumab is a fully-human IgG monoclonal antibody that binds with PD-1, a checkpoint receptor expressed on activated T cells [1]. As such, it is classified as an immune-checkpoint inhibitor (ICI) along with ipilimumab, a fully-human anti-CTLA4 monoclonal antibody. It works by preventing PD-1

![Figure 4](image1.png)

**Figure 4.** Nivolumab-associated colitis in remission with mucosal healing. Endoscopic remission: (A) cecum, (B) sigmoid colon, (C) rectum. Histologic remission: (D) cecum, (E) sigmoid colon, (F) rectum.

![Figure 5](image2.png)

**Figure 5.** The colonoscopy revealed that nivolumab-associated colitis relapsed following mucosal healing. (A) cecum, (B) transverse colon, (C) descending colon, (D) proximal sigmoid colon, (E) distal sigmoid colon, (F) rectum.
on T cells from binding with PD-1 (PD-L1/PD-L2) on cancer cells, thereby reactivating antigen-specific T cells that were not responding to the cancer cells [9]. With the novel mechanism of action of nivolumab, newer indications for its use continue to be added, and it is being used in increasing the number of cases. Nevertheless, nivolumab has also been associated with various immune-related adverse events (irAEs). The most prevalent irAEs are skin disorders, occurring in 17% of cases [10,11].

IrAEs associated with digestive organs are also most major as well as dermal toxicities. Intestinal inflammation with symptoms occurs most frequently from approximately sixth cycles after initial treatment [11,12]; therefore, the disease progression in the present case was a typical clinical course. Nivolumab-associated colitis resembles UC endoscopically and histopathologically [13]. So, it is extremely difficult to distinguish completely between irAE-associated colitis and primary UC. In pathologically, a previous report showed two types of irAE colitis; colitis of the lymphocytic type and colitis with epithelial apoptosis [12]. In our case, apoptotic epithelial cells were not seen in the crypts at onset. However, a few apoptotic cells were observed in biopsy specimens at two-months after colitis-onset (data not shown) and at relapse. The difference between two pathological types might be related to the phase of irAE colitis. Furthermore, based on detailed pathological observation, the

Figure 6. Histologic findings at relapse stage. In rectum, apoptosis cells were seen in the crypt (the arrow). (A) cecum, (B) transverse colon, (C) descending colon, (D) proximal sigmoid colon, (E) distal sigmoid colon, (F) rectum.

Figure 7. Clinical course. Six months after the steroids discontinuation, the patient’s fecal immunochemical test (FIT) and fecal calprotectin (CPT) values started to increase. Diarrhea by relapsed colitis was improved after treatment with mesalazine.
number of crypts did not decrease extensively. In fact, the crypt density was maintained not only at onset but also at relapse. In the present case, it is characteristic finding that crypt atrophy during every phase: onset, remission, and relapse were less than typical UC.

In case reports concerning nivolumab use, all patients had advanced cancers. To date, nivolumab has been administered to patients who were not responsive to conventional chemotheraphy; hence, many of these patients had a low chance of long-term survival. Thus, there may have been insufficient consideration regarding whether long-term maintenance treatments for irAEs are necessary or not. Generally, moderate or severe irAE colitis at maintenance treatments for irAEs are necessary or not. However, the anti-cancer effect of nivolumab persisted in the long-term, even when administration is discontinued [14]. The initial treatment for the irAE is well established; nevertheless, it is unclear whether maintenance therapies are effective or not after induction of remission. In maintenance treatments for UC, major drug is mesalazine. Given the powerful efficacy of nivolumab, it is reasonable to expect a higher number of long-term survival cases in the future. Because remission was observed in the present case, we suggest mesalazine as a key drug to keep remission of irAE colitis.

In the present case, irAE colitis relapsed after achievement of mucosal healing suggesting the persistence of irAEs. The anti-cancer effect of nivolumab was also maintained while the irAEs occurred; however, the anti-cancer effect of nivolumab was lost after the irAEs disappeared. It has been reported that anti-cancer effect of nivolumab persists in the long-term, even when administration is discontinued [15]. Because of its durable pharmacological action, nivolumab markedly differs from conventional drugs, whose duration of action can be estimated from their half-lives or metabolic pathways. The results from five-year follow-up cohort of patients treated with nivolumab, revealed that twelve (54.5%) of 22 nivolumab responders who received no further therapy were long survivors without cancer progression [16]. In addition, randomized phase II and III trials of nivolumab and ipilimumab showed that progression-free survival (PFS) and overall survival (OS) seemed similar between patients who discontinued treatment because of irAEs and those who did not discontinue because of irAEs [15]. Osa et al. reported that prolonged nivolumab binding on T cells was detected more than 20 weeks after infusion from peripheral blood in patients with non-small cell lung cancer [17]. Therefore, the detection of irAEs caused by ICIs might indicate that anti-cancer effects will persist after discontinuing ICI. Based on the information, irAE colitis could occur after discontinuing nivolumab.

In colitis, the most accurate method of follow-up is colonoscopy. However, frequent endoscopy is physically burdensome for cancer patients. Therefore, it is necessary to consider an alternative monitoring procedure, one that is minimally invasive. FIT and CPT values involve simple tests for both patients and clinician. The present case suggests that regularly monitoring FIT and CPT provides an effective biomarker for assessing disease activities. Because of the increasing possibility of relapse, we suggest monitoring of FIT or CPT every clinic-visit or once a month especially after the withdrawal of steroid. The elevation of FIT values in the presence of mild symptoms can act as a significant sign for detecting the activity of irAE colitis.

In conclusion, the irAE colitis could relapse after achievement of mucosal healing. Tight monitoring of FIT and CPT can lead to an early treatment with mesalazine; this, in turn, will help better maintain the quality of life.

Disclosure statement

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