

[CASE REPORT]

Readministration of Nivolumab after Persistent Immune-related Colitis in a Patient with Recurrent Melanoma

Yosuke Fujii¹, Yoshitaka Nishikawa^{1,2}, Motoo Nomura¹, Shin'ich Miyamoto³, Yu Uneno¹,
Takahiro Horimatsu¹ and Manabu Muto¹

Abstract:

Nivolumab shows promising efficacy against metastatic melanoma. However, immune-related adverse events are of great concern. We herein report a case of persistent colitis that developed during nivolumab monotherapy and nivolumab readministration. An 82-year-old Japanese woman with recurrent melanoma developed Grade 3 colitis after 6 cycles of nivolumab. She was treated with corticosteroid for 28 days. Follow-up by computed tomography and colonoscopy after corticosteroid treatment revealed persistent pancolitis. Her symptoms ameliorated spontaneously in two months. Given the amelioration, nivolumab was restarted and resulted in the maintenance of stable disease for 21 months without recurrence of colitis. Even in cases of persistent colitis over several months, nivolumab readministration should be considered.

Key words: PD-1 inhibitor, immune-related adverse event, readministration, colitis, melanoma

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Introduction

Nivolumab, a programmed cell death protein 1 (PD-1) inhibitor, shows promising efficacy in patients with metastatic melanoma and other solid tumors. However, systemic immune-related adverse events (irAEs), such as interstitial lung disease, liver dysfunction, hypothyroidism, and colitis, are of great concern (1). Approximately 30% of patients develop nivolumab-associated colitis (Common Terminology Criteria for Adverse Events v4.0; CTCAE, any Grade), and less than 10% of patients have severe colitis (Grade 3 or 4). Nivolumab-associated colitis generally occurs one to three months after starting nivolumab therapy (2). As irAEs can occasionally be lethal, the readministration of nivolumab after a severe irAE has been controversial. We herein report a case of restarting nivolumab after recovery from nivolumab-associated colitis.

Case Report

An 82-year-old Japanese woman was admitted to our hospital with intermittent severe abdominal pain. She had a history of malignant rectal melanoma treated with transanal tumor resection and 6 subsequent cycles of adjuvant chemotherapy (dacarbazine, nimustine, and vincristine: DAV) 15 years earlier. Four years after the first episode, relapse of the primary rectal lesion was found. With transanal tumor resection and DAV therapy, periodical gallium scintigraphy confirmed no tumor residue. She had been followed-up for three years after the relapse and had finished her periodical checkups seven years earlier.

Four months before admission, she noticed bloody stool. Colonoscopy revealed the recurrence of rectal melanoma at the primary site with pathological confirmation, and computed tomography (CT) detected multiple lesions of para-aortic lymph nodes, lung, liver, and the first lumbar verte-

¹Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Japan, ²Department of Health Informatics, School of Public Health, Kyoto University, Japan and ³Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Japan

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Correspondence to Dr. Yoshitaka Nishikawa, ynishikawa-ty@umin.ac.jp



Figure 1. CT image. (A) The cecal wall was markedly thickened (arrowheads) at the onset of colitis on the day of admission. (B) The thickened cecal wall was improved on day 21 of corticosteroid treatment. (C) Recurrence of thickened cecal wall three weeks after corticosteroid treatment was discontinued.

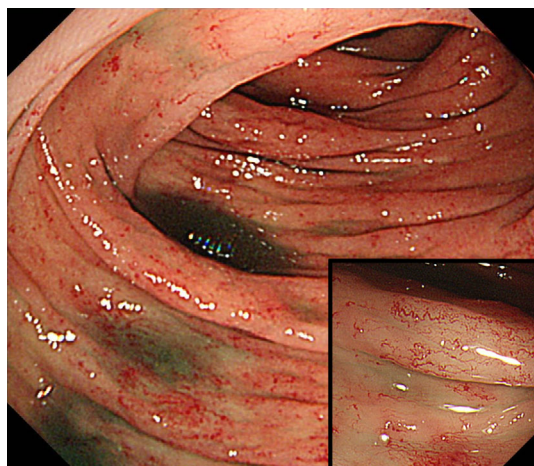


Figure 2. Colonoscopy images after the discontinuation of corticosteroid treatment. Erythematous mucosa and dilated small vessels (inset).

bra. We detected no other malignancy. Given the recurrence at the rectal primary site and simultaneous multiple lesions on CT, she was diagnosed with recurrent melanoma with multiple metastasis to the liver, lung, para-aortic lymph node, and first lumbar vertebra. Her Eastern Cooperative Oncology Group performance status was 0. She was administered nivolumab (2 mg/kg) every 3 weeks. After completing six cycles of nivolumab, she developed severe abdominal pain and loose bloody stool twice per day and was referred to our hospital.

She had a sudden onset of a fever (38.1°C) the day before admission to our institution. A physical examination revealed abdominal tenderness from the left hypochondriac to the lower quadrant region. Laboratory findings showed an increased white blood cell count (12,400/mm³, neutrophils 87%), C-reactive protein level (CRP, 23.0 mg/dL) and decreased hemoglobin (9.7 g/dL). Nuclear antibodies and anti-neutrophil cytoplasmic antibodies were negative. Contrast-enhanced CT on the day of admission showed that the colonic wall from the cecum to the transverse colon was markedly edematous and thickened (Fig. 1A), which is not consistent with ischemic colitis, as this typically occurs in a localized region, such as the splenic curvature, due to a reduced blood supply from the major arteries. We excluded in-

fectious colitis due to the following clinical findings: Both blood and stool cultures were negative for pathogenic bacteria, and serum testing of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. These clinical findings and the history of nivolumab therapy suggested an association between colitis and nivolumab therapy. Colonoscopy could not be performed because of severe abdominal pain and the risk of perforation at that time. Colonoscopy was therefore planned after the amelioration of her symptoms.

The patient discontinued nivolumab and was immediately treated with intravenous prednisolone 2 mg/kg/day combined with antibiotics according to the manufacturer's management guidelines (1). Her abdominal tenderness was relieved in the next day and completely ameliorated after one week. The blood in her stool was resolved, and loose stool once a day was observed until six days after admission. Her hemoglobin level improved from 9.7 g/dL to her baseline level (12 g/dL) after 1 week without blood transfusion. Prednisolone was gradually tapered every three days. As her symptoms were ameliorated, colonoscopy was performed on day 9 after admission, revealing pancolitis from the ileum to the descending colon with reddish, edematous erythematous mucosa. Histopathology revealed interstitial edema and inflammatory infiltration of lymphocytes, plasma cells, eosinophils, and neutrophils. The typical findings of ischemic colitis, such as ghost outlines and atrophy of crypt and interstitial eosinophilic deposition, were absent. We confirmed the diagnosis of nivolumab-associated colitis. Three weeks after starting prednisolone treatment, CT revealed that the thickened cecal wall was ameliorated (Fig. 1B). She was discharged on day 22 of hospitalization with prednisolone reduced to 5 mg/day. Corticosteroid treatment was continued for 28 days.

Three weeks after the discontinuation of corticosteroid treatment, she still complained of loose stool. Follow-up CT on day 50 after the first admission revealed recurrent edematous and thickened cecal wall (Fig. 1C). Colonoscopy on day 59 after the first admission showed pancolitis from the ileum to the descending colon with reddish, edematous erythematous mucosa, and a loss of normal vascularity (3, 4) (Fig. 2). A histopathological examination of the biopsy specimen revealed mild inflammation with eosinophilic

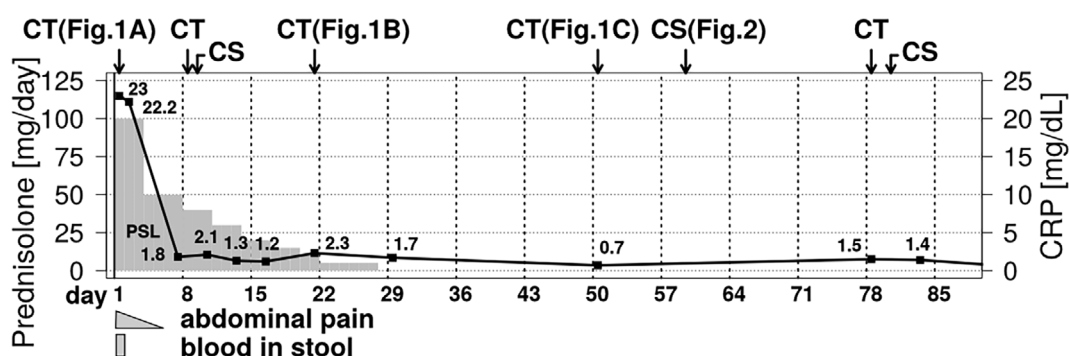


Figure 3. The clinical course of this patient. CT: computed tomography, CS: colonoscopy, PSL: prednisolone

infiltration in the cecal mucosa (3, 4) and reconfirmed no evidence of pathogens, including CMV and *Mycobacterium tuberculosis*. These findings were consistent with recurrence of irAE colitis. To relieve discomfort, the rectal recurrent lesion was endoscopically dissected, confirming the diagnosis of recurrent melanoma without a v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutation.

Careful observation was carried out without reintroduction of corticosteroids (Fig. 3). Follow-up colonoscopy on day 80 after admission confirmed persistent pancolitis with edematous erythematous mucosa. The CRP level remained slightly elevated at around 1.5 mg/dL. It gradually decreased to 0.3 mg/dL, and her loose stool improved spontaneously 2 months after the discontinuation of corticosteroids. With stable clinical symptoms and a normal CRP level, nivolumab was restarted on day 99 after admission. Her condition has remained stable for 21 months without recurrence of irAE colitis or progression of the disease (more than 20% increase in tumor volume or new metastatic lesions).

Discussion

To our knowledge, this is the first case of nivolumab-associated colitis with successfully restarted nivolumab after the recovery from colitis. In the present case, colitis lasted more than three months, including corticosteroid tapering, which was longer than the one month stated in the guidelines (1).

Our patient was followed up carefully after the development of Grade 3 irAE colitis with nivolumab monotherapy. Discontinuation of nivolumab and immunosuppressive therapy (corticosteroid) successfully relieved her symptoms. Corticosteroid administration was gradually tapered over one month. The CT and colonoscopy findings were more severe than the clinical symptoms (i.e. loose stool and abdominal pain) and CRP elevation (<1.5 mg/dL). This case suggests that periodical visits, an in-depth history taking, and careful CRP monitoring combined with CT imaging can assist in the early detection and follow-up of irAE colitis in the clinical setting.

The persistence of colonic inflammation in this 82-year-

old patient suggested that colitis could last for over 3 months. For irAE colitis, the management guidelines recommend continuing steroids until recovery to Grade 1 and then tapering the dose over at least one month (1). Previous clinical studies have reported that irAE colitis was sustained for less than 1 month [median 0.7 weeks (5) and 4.0 weeks (6)]. While some factors have been reported to be associated with the clearance of nivolumab, further investigation is needed to ensure the safe administration of nivolumab.

The readministration of nivolumab was performed in this case after recovery from severe irAE colitis. With careful observation of clinical symptoms and laboratory data, the patient has maintained a stable condition for 21 months without recurrence of colitis. The readministration of nivolumab after irAEs has been controversial. A previous study reported that 7 out of 20 patients who developed irAE pneumonitis restarted nivolumab, and 5 patients successfully continued without recurrence of irAE pneumonitis (7). With regard to ipilimumab, an early approved immune-checkpoint inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA4), the accumulation of informative clinical data has indicated that ipilimumab-associated colitis is more frequently observed than nivolumab-associated colitis (8). A previous study reported the successful use of nivolumab after ipilimumab-induced colitis for 11 unresectable metastatic melanoma cases (3 Grade 2, 7 Grade 3, and 1 Grade 4) (9). Another study reported 67 advanced melanoma patients with a history of ipilimumab-induced irAE, and 47 cases of colitis (5 Grade 2, 37 Grade 3, and 5 Grade 4) treated with nivolumab attained an average progression-free survival (PFS) of 7.2 months. It was also reported that recurrence of the same irAE was rare (3%, 2/67 cases), even in patients with severe colitis (10). Although molecular immunological evidence was not available in previous reports and this case, the clinical findings suggest that recurrence of irAE at the same organ is not common (10). Thus, readministration can be considered under careful observation. In the present case, restarting nivolumab was the only treatment option, as cytotoxic drugs had already been administered and there was no BRAF mutation.

With the readministration of nivolumab, our patient successfully maintained stable disease status for 21 months. The present case suggests that the readministration of nivolumab may be a feasible treatment option, even in cases of persistent irAE colitis over a few months.

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

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