Safe Use of Nivolumab in a Patient with Epipharyngeal Carcinoma and Preexisting Ulcerative Colitis: A Histologically Proven Case Report

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Abstract:
Nivolumab, an antibody against human programmed cell death 1 (PD-1), enhances pre-existing immune responses and has antitumor activity. However, it may also cause undesirable immune-related adverse events (irAEs), such as anti-PD-1-related colitis. In addition, Nivolumab can worsen pre-existing autoimmune diseases. Ulcerative colitis (UC) is a chronic inflammatory disease of the colon. Its exact cause is unknown, but it may involve the dysregulation of the mucosal immune response. Thus, it is of great interest whether nivolumab can affect UC activity. This is the first report of a patient with epipharyngeal carcinoma and ulcerative colitis who was confirmed to have been safely treated with nivolumab based on autopsy findings.

Key words: anti-PD-1 antibody, nivolumab, ulcerative colitis, immune-related adverse event (irAE), 5-aminosalicylic acid (5-ASA)

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Introduction

Immune checkpoint antibodies, which block cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) pathways and enhance pre-existing immune responses, have demonstrated antitumor activity and have been approved for the treatment of various malignancies (1-3).

Nivolumab is a fully human IgG4 monoclonal antibody that is specific for human PD-1 and which inhibits the binding of PD-L1 and PD-L2 to the PD-1 receptor. The binding of these ligands to PD-1 receptors on T cells impedes T cell proliferation and activation and cytokine production, thus inhibiting the immune response to tumors. Nivolumab can therefore potentiate immune reactions and mediate antitumor activity (4, 5). Nivolumab was demonstrated to be active in non-small lung carcinoma (2), melanoma (6, 7), renal-cell carcinoma (8), Hodgkin’s lymphoma (9), and recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), and was approved by the FDA after a pivotal phase III trial (10).

A major limitation of nivolumab is that its specific pharmacological function may lead to unrestrained activation of effector immune responses and a reduction of anti-inflammatory effects, resulting in undesirable autoimmune-type manifestations called immune-related adverse events (irAEs) (11). These reactions can occur in every organ, but mainly appear as skin disorders, pneumonitis, endocrine disorders, gastrointestinal disorders, and hepatobiliary disorders. Anti-PD-1-related colitis is a major irAE that manifests as diarrhea and colitis. In a clinical trial, grade 3-4 colitis was reported in 1-2% of patients who received anti-PD-1 therapy (12). An additional drawback of immune checkpoint inhibition is that it can worsen pre-existing autoimmune diseases (13).

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that leads to diarrhea, hematochezia, abdominal pain, and malnutrition. The exact cause of this disease is still unknown, but it seems to involve dysregulation of the
mucosal immune response, resulting in an imbalance between regulatory (Treg) and effector T cells (14). Thus, it is of great interest whether an PD-1 antibody affects the activity of UC. We herein report the case of a patient with both epipharyngeal carcinoma and UC, who was safely treated with nivolumab.

Figure 1. The diagnosis of active UC. (A) Colonoscopy revealed active colitis throughout the colon. Congestive, edematous, and erosive mucosa with friability and spontaneous bleeding were observed in the sigmoid colon. (B) A biopsy specimen from the sigmoid colon showed inflammatory cell infiltration, distortion, and crypt inflammation. These endoscopic and pathological findings were consistent with active ulcerative colitis.

Figure 2. Endoscopic findings (sigmoid colon). Endoscopy before chemotherapy showed UC in remission with no apparent active inflammation.

Case Report

The patient was a 52-year-old woman who was a non-smoker and non-drinker, who was diagnosed with epipharyngeal carcinoma with extensive intracranial infiltration and persistent headache in November 2015. A histological examination showed moderately differentiated squamous cell carcinoma (clinical stage, cT4bN0M0). The patient had been diagnosed with ulcerative colitis in 2012, and had been successfully treated with 5-ASA. She had persistent diarrhea and progressive anemia at the time of the diagnosis of epipharyngeal carcinoma; thus, colonoscopy was performed (Fig. 1), which revealed highly active pancolitis-type UC (Mayo score 10). Chemoradiotherapy for epipharyngeal carcinoma was planned at the time of the diagnosis, but treatment for UC was prioritized. Sequential steroid administration and granulocyte and monocyte adsorption apheresis were conducted. The treatments successfully induced the remission of the patient’s UC, and 5-ASA maintenance therapy (4 g/d) was subsequently initiated. Due to the risk of toxicity affecting the colonic mucosa, chemotherapy was withheld, and radiotherapy (total dose, 70 Gy) was performed from January to March 2016. The epipharyngeal tumor shrunk and the patient’s headache was relieved. At the end of 2016, low back pain appeared, and multiple bone metastases were diagnosed in March 2017. The patient received palliative radiotherapy for the painful metastases (doses: right iliac crest, 20 Gy; left femur, 30 Gy). Recurrent epipharyngeal carcinoma and multiple bone tumors were detected by PET-CT in April 2017.

The patient visited our hospital in June 2017 to determine whether she was eligible for chemotherapy given her continuously asymptomatic UC. We confirmed the stable remission of UC by colonoscopy (Fig. 2) and the appearance of new liver metastases by computed tomography (CT). We judged that chemotherapy was viable. CDDP/SFU (Cisplatin [100 mg/m²], IV over 2 hours on Day 1] followed by 5-fluorouracil [1,000 mg/m², CIV 24 hours on Days 1-4, q3 w]) was administered as first-line therapy. Partial remission was initially achieved; however, after six courses, her liver and bone metastases progressed. Thus, second-line chemotherapy was initiated with paclitaxel (PTX [100 mg/m² IV, over 1 hour on Day 1, repeated every 6 weeks]) was started in December 2017. CT of the liver performed at two months after the start of PTX showed a mixed response, and the administration of PTX was continued until tumor growth was demonstrated definitively in April 2018. The patient’s treatment schedule is shown in Fig. 3. After reaffirming the state of UC remission (Mayo score, 0), nivolumab (3 mg/kg, every 2 weeks) was given as third-line chemotherapy from May 2018. After three
Figure 3. The clinical course. PTX: paclitaxel, CDDP: cisplatin, 5-FU: 5-fluorouracil, LCAP: leukocytapheresis

A  B

Figure 4. Autopsy findings. (A) Macroscopic observation revealed a slightly erythematous mucosa in the colon. (B) Microscopic observation of the sigmoid colon revealed blood congestion manifesting as an erythematous mucosa, mild lymphocytic infiltration, and fibrosis, but there were no signs of active UC or irAEs secondary to colitis.

courses, CT demonstrated rapid growth of the patient’s liver metastases but bone scintigraphy revealed a decreased number of skeletal metastases. During these therapies, the patient did not experience diarrhea or other symptoms indicative of irAE colitis or the recurrence of UC. Because of her hyperprogressive liver disease, supportive care was chosen. Her condition rapidly worsened, and she died two weeks after the start of palliative care intervention.

An autopsy performed seven weeks after the first administration of nivolumab revealed the following findings. There was no evidence of tumor in the pharynx, indicating the effectiveness of radiation and chemotherapy at the primary site. Multiple metastases were found in the liver and bones. While most of the liver tumors were viable, approximately half of the bone tumors had undergone necrosis, indicating a mixed tumor response to the treatments. The remaining tumors were negative for PD-L1. In the colon, mild lymphocytosis, minimal neutrophil infiltration, a conserved crypt structure, and slight fibrosis were observed, none of which suggested the recurrence of UC or anti-PD-1-related colitis (Fig. 4). It was concluded that nivolumab had been used safely to treat this patient with preexisting UC.

Discussion

The rates of anti-PD-1-induced diarrhea and colitis are reported 17.2% and 1.1% respectively (15). Anti-PD-1-associated colitis exhibits a variety of macroscopic findings, from normal to severe inflammatory changes such as exudates, granularity, erythema, loss of vascularity, and ulcerations (16, 17), which are somewhat similar to those of UC. The common histopathological features of anti-PD-1-associated colitis are neutrophilic crypt microabscesses and cryptitis, increased crypt epithelial cell apoptosis, and the
presence of crypt atrophy and dropout (16, 17).

UC is an idiopathic inflammatory disorder that affects the colorectum. Endoscopic findings typically show erythema, loss of the normal vascular pattern, granularity, erosion, friability, bleeding, and ulceration (18, 19). Histological findings include distortion of the crypt architecture, crypt shortening, increased numbers of lymphocytes and plasma cells in the lamina propria, mucin depletion, and Paneth cell metaplasia (18, 19).

The exact causes of both irAE colitis and UC are still unknown, but blood analyses in patients with immune checkpoint inhibitor-induced colitis revealed a decrease in regulatory T cells and an increase in effector T cells (20), which is similar to the T cell imbalance seen in UC patients (21). Additionally, polymorphisms of the CTLA-4 gene were reported to be associated with susceptibility to both Crohn’s disease and UC (22). Thus, the potential for immune checkpoint inhibitors to exacerbate UC is a particular concern.

Because patients with pre-existing autoimmune disorders are excluded from trials evaluating immune checkpoint inhibitors, few data are available on the risk of immune-related colitis in patients with pre-existing inflammatory bowel disease (IBD). Previous studies reported a risk of approximately 30% for relapse of pre-existing IBD after treatment with anti-CTLA-4 antibodies [13, 23, 24]. Only one report showed that anti-PD-1 therapy did not evoke flares of underlying IBD in three patients with CD and in two patients with UC and prior colectomy (24). There are no reports thus far about the use of anti-PD-1 in unoperated UC patients. In addition, histological examinations were not usually performed after immune checkpoint inhibitor treatment in previously reported cases. In this study, a histological assessment during the autopsy of a cancer patient with preexisting UC proved that there was no nivolumab-induced flare of UC or colitis in the colon.

Although the median time to the onset of symptoms in patients with immune-related gastrointestinal events (mainly diarrhea and colitis) was around week 8 for nivolumab treatment (15), a recent report showed that nivolumab-induced colitis was diagnosed within 7 weeks in more than 50% of cases (25). Based on this report, we consider that our observation period of 7 weeks was acceptable to conclude that nivolumab was safely used in the treatment of our patient with preexisting UC.

In this case, the patient had taken 5-ASA as maintenance therapy for UC. 5-ASA is the most frequently used drug in the treatment of UC, and is considered to exert an anti-inflammatory action via the increased expression of peroxisome proliferator-activated receptors in gastrointestinal epithelial cells (26). Orally administered 5-ASA has been shown to suppress the immune response and anti-inflammatory effect directly in the colon mucosa. The anti-inflammatory effect of 5-ASA might prevent the exacerbation of UC or immune checkpoint inhibitor-induced colitis. In fact, 5-ASA treatment was reported to improve the frequency of diarrhea and endoscopic findings in a patient with immune checkpoint inhibitor-induced colitis (27). Moreover, after it is absorbed, 5-ASA is metabolized extensively to N-Ac-5ASA, by the N-acetyltransferase 1 (NAT 1) in intestinal epithelial cells and the liver. This metabolite was reported to be inactive (28). Thus, 5-ASA is considered not to affect the efficacy of nivolumab. Considering its relatively low incidence of side effects, 5-ASA might be effective for the treatment and prevention of immune checkpoint inhibitor-induced colitis. Further studies are needed to confirm this hypothesis.

Although the patient also received dexamethasone once at a dose of 6.6 mg as a premedication of PTX, it is thought the effect was limited because the half-life of dexamethasone is approximately 36 hours.

In this study, the use of nivolumab in the treatment of HNSCC was proven to be safe, with no serious adverse events or UC flare. This is the first report of a histological examination following nivolumab therapy in an unoperated patient with preexisting UC.

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

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions
YH, YM, and LAL interacted with the patient. YM and YH wrote the manuscript. LAL designed and generated all figures. YO prepared pathology slides and analyzed the pathology. KT, LAL, YM, and HY reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The patient’s family provided their consent for the publication of the data associated with the present case.

References
1. Hodi FS, O’Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723, 2010.
2. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Non-Squamous Non-Small-Cell Lung Cancer. N Engl J Med 373: 1627-1639, 2015.
3. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372: 2018-
Maul J, Loddenkemper C, Mundt P, et al. Peripheral and intestinal
Hassel JC, Heinzerling L, Aberle J, et al. Combined immune
Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab Therapy in
Villadolid J, Amin A. Immune checkpoint inhibitors in clinical
Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Re-
Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic
Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM,
Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM,
Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 377: 1345-1356, 2017.
Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373: 1803-1813, 2015.
Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin’s lymphoma. N Engl J Med 372: 311-319, 2015.
Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 375: 1856-1867, 2016.
Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366: 2443-2454, 2012.
Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res 4: 560-575, 2015.
Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncol 2: 234-240, 2016.
Maul J, Loddenkemper C, Mundt P, et al. Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. Gastroenterology 128: 1868-1878, 2005.
Hassel JC, Heinzerling L, Aberle J, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): Evaluation and management of adverse drug reactions. Cancer Treat Rev 57: 36-49, 2017.
Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies. Am J Surg Pathol 41: 643-654, 2017.
Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: case series and appraisal of ‘immunomodulatory gastroenterocolitis’. Histopathology 70: 558-567, 2017.
Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 7: 982-1018, 2013.
Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 105: 501-523; quiz 524, 2010.
Nancey S, Boschetti G, Cotte E, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab is associated with a profound long-lasting depletion of Foxp3+ regulatory T cells: a mechanistic explanation for ipilimumab-induced severe enterocolitis? Inflamm Bowel Dis 18: E1598-1600, 2012.
Hanai H, Iida T, Ikeya K, et al. A new paradigm in ulcerative colitis: regulatory T cells are key factor which induces/exacerbates UC through an immune imbalance. Mol Immunol 54: 173-180, 2013.
Zhang M, Ni J, Xu WD, et al. Association of CTLA-4 variants with susceptibility to inflammatory bowel disease: a meta-analysis. Hum Immunol 75: 227-233, 2014.
Kahler KC, Eigentler TK, Gesierich A, et al. Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. Cancer Immunol Immunother 67: 825-834, 2018.
Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol 28: 368-376, 2017.
Yamauchi R, Araki T, Mitsuyama K, et al. The characteristics of nivolumab-induced colitis: an evaluation of three cases and a literature review. BMC Gastroenterol 18: 135, 2018.
Rousseaux C, Lefebvre B, Dubusquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Exp Med 201: 1205-1215, 2005.
Kubo K, Kato M, Mabe K. Nivolumab-Associated Colitis Mimicking Ulcerative Colitis. Clin Gastroenterol Hepatol 15: A35-A36, 2017.
van Hogezaad RA, van Hees PA, van Gorp JP, et al. Double-blind comparison of 5-aminosalicylic acid and acetyloyl-5-aminosalicylic acid suppositories in patients with idiopathic proctitis. Aliment Pharmacol Ther 2: 33-40, 1988.