症例報告

A CASE OF NIVOLUMAB-INDUCED IMMUNE-RELATED ADVERSE EVENT IN THE UPPER GASTROINTESTINAL TRACT IN RECURRENCE/METASTATIC HEAD AND NECK CANCER

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Abstract.
A 61-year-old male patient underwent partial glossectomy and right neck dissection for tongue cancer cT2N1M0. Because of the locoregional recurrence, the patient received neoadjuvant chemotherapy followed by subtotal glossectomy, neck dissection, and reconstruction. However, new locoregional lesions and distant metastasis were detected during postoperative chemotherapy. Seven courses of nivolumab were administered, but the tumor grew. Hence, the chemotherapy regimen was switched to paclitaxel and cetuximab. After eight courses of this regimen, leakage of liquid enteral nutrients around the gastrostoma began, and the patient was hospitalized urgently due to severe abdominal distension and nausea. Upper gastrointestinal endoscopy revealed edematous esophageal and gastric mucosa covered with white coating spots. Histopathological examination of the duodenal mucosa specimen showed CD8-+ natural killer (NK) T-cells infiltrating the lamina propria mucosae, which corresponded with an immune-related adverse event (irAE). Pulse steroid therapy significantly improved the findings of upper gastrointestinal endoscopy and symptoms.

Key words: immune-related adverse event, nivolumab, upper gastrointestinal tract, immunostaining, CD8-positive T-cell, pulse steroid therapy

Introduction

The immune checkpoint consists of cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death protein 1 (PD-1), and ligand for PD-1 (PD-L1). They are essential for antitumor immunity, anti-infection, and autoimmunity [1-3]. Immunotherapy has become a new treatment option for

recurrence/metastatic cancer. T cells have a PD-1 and checkpoint protein which prevent them from attacking the body's own cells by binding PD-1. CTLA-4 functions also regulate the T cell function. Tumor cells, however, are able to evade the immune system and grow freely by binding to PD-1. Nivolumab, a human monoclonal antibody against human PD-1, one of the immune checkpoint inhibitors (ICIs), was approved in 2017 for treating unresectable locoregional recurrence or metastatic lesions in Japan. Although ICIs activate endogenous antitumor immunity, they can also activate immune responses against autologous organs and cause organ damage, leading to various irAEs, depending on the target organ. Typical examples are interstitial pneumonia, liver dysfunction, colitis, endocrine disorders, and type 1 diabetes. In most cases, irAEs can be controlled by early detection and steroid administration or hormone replacement therapy, but hepatic dysfunction and colitis may require more aggressive immunosuppressive therapy [4].

In this case, we experienced massive leakage around the gastrostoma, difficulty in continuing enteral nutrition, and remarkable hypoproteinemia, that were caused due to an irAE of the upper gastrointestinal tract.

Case report

a. A 61-year-old man had a history of cholecystectomy for chronic cholecystitis. He had a 21-year history of smoking (20 cigarettes/day for 20 years and 20 e-cigarettes/day for 1 year) and a 41-year history of consuming alcohol (40 grams pure alcohol/day).

b. History of present illness

The patient who had been suffering from pain in a site on the right side of the tongue for 10 months visited a neighboring ENT clinic and was referred to our institution due to the suspicion of tongue cancer.

At the time of the first visit to our institution, a biopsy specimen of the tongue tumor revealed a highly differentiated squamous cell carcinoma, and imaging studies confirmed the diagnosis of tongue cancer, cT2N1M0 cStage III (UICC 8th edition). Twenty days after the initial diagnosis, the patient underwent right partial glossectomy and right neck dissection. However, locoregional recurrence was pointed out 2 months later. X-ray computed tomography (CT) revealed rapid growth of the tumor. Neoadjuvant chemotherapy with DCF (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and 5-FU 750 mg/m^2) was followed by subtotal glossectomy, reconstruction (anterolateral thigh flap), neck dissection, and tracheostomy for the treatment of cancer. Although postoperative chemoradiation with cisplatin (40 mg/m^2/week) was also employed as an adjuvant therapy, local recurrence and metastases (lung and brain) occurred during the treatment. According to the numerous discussions conducted among head and neck surgeons, oncologists, and radiotherapists, chemoradiation was discontinued at 26 Gy plus three courses of cisplatin. And then, nivolumab (240 mg/2 weeks) was initiated. Even after seven courses of nivolumab, the lesions were still growing, so the chemotherapy regimen was switched to paclitaxel (80 mg/m^2/week) and cetuximab (400 mg/m^2/week for the first course and 250 mg/m^2/week for the second and subsequent courses). Although tumor slight regression was observed at the end of eight courses of paclitaxel and cetuximab, liquid enteral food began to leak around the gastrostomy, and the patient vomited after feeding. After 3 months of the discontinuation of nivolumab, although irAE

was unexpected, the patient suffered from upper gastrointestinal symptoms.

Upper gastrointestinal endoscopy revealed that mucosae of the esophagus and stomach were edematous, bled easily, and covered with white spots (Fig. 1 A, B). The duodenal mucosa was mildly edematous with scattered erosions. As a result of many discussions with gastroenterologists, we changed the gastrostomy tubes and treatments around the gastrostoma, but the patient's condition did not improve. Despite discontinuing tube feeding and changing the nutritional support to parenteral nutrition, leakage around the gastrostomy tube did not improve. An unexpected increase in inflammatory response, hypoproteinemia, and diarrhea (1 to 3 times a day) appeared. No melena was observed. Fifteen weeks after discontinuation of nivolumab, CT showed shrinkage of lung metastases (Fig. 2). One month after emergency hospitalization, the patient was in shock and was admitted to the intensive care unit (ICU). Blood tests showed C-reactive protein (CRP) of 23.7 mg/dl, white blood cell count of 10730/ μ l, albumin of 1.1 g/dl, creatinine of 3.08 mg/dl, and blood urea nitrogen (BUN) of 39.3 mg/dl. CT revealed an intestinal perforation, but the location and cause of the perforation were unclear.

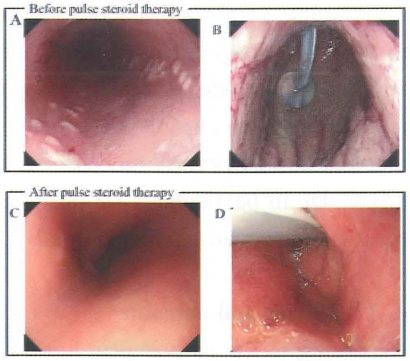

Fig.1. Findings of gastrointestinal endoscopy
The esophageal mucosa was partially covered with white spots (A). The gastric mucosa was edematous and bled easily (B). After pulse steroid therapy, the white spots on the esophageal mucosa disappeared and the mucosa was endoscopically normal (C). Edema of the gastric mucosa also improved (D).

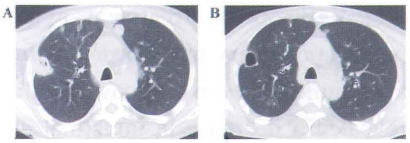

Fig.2. Reduction of lung metastasis
Chest CT at the end of 7 courses of nivolumab revealed increased lung metastases (A). 7 weeks after discontinuation of paclitaxel and cetuximab chemotherapy, the lung metastases were clearly reduced (B).

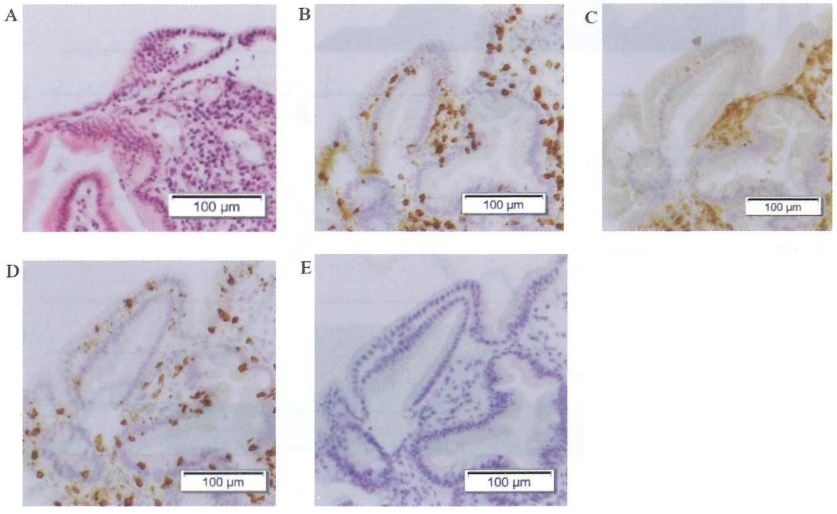

Fig.3. Histopathological findings of the duodenal mucosa specimen
Hematoxylin and eosin staining (A) followed by immunostaining (B: CD3, C: CD8, D: CD4, E: CD20) were helpful for confirming the diagnosis of an immune-related adverse event.

A sample of gastric mucosa taken during upper gastrointestinal endoscopy upon admission to the ICU was highly inflamed and had unevaluable necrotic tissue. Hematoxylin and eosin staining of a duodenal mucosa sample proved destruction and regeneration of cryptic fossae, as a result of which chronic drug-induced inflammation was suspected (Fig. 3 A). Furthermore, the mucosal lamina propria mucosae was infiltrated with CD3-, CD4-, and CD8-positive T-cells (Fig. 3 B, C, D). In particular, CD8-positive T-cells infiltrated crypts, indicating a strong inflammatory reaction. However, CD20-positive B-calls were hardly observed (Fig. 3 E).

c. Treatment and outcome

According to the pathological findings stated previously, it was thought that a series of digestive symptoms were nivolumab-induced irAE, which caused persistent hypoproteinemia. Therefore, at the suggestion of our oncologists, pulse steroid therapy (1000 mg/day of methylprednisolone for 3 days) was given to the patient.

The amount of leakage around the gastrostoma was 1300 ml/day on the day before pulse steroid therapy, but the daily total amount dramatically decreased to 20 ml on the fourth day after pulse steroid therapy, and diarrhea symptoms (1–3 times/day [Grade 1]) also improved (Fig. 4). Before the treatment, hypoalbuminemia required the use of several bottles of albumin preparation every day. However, after the treatment, there was no significant decrease in serum albumin levels even without the administration of albumin preparation (Fig. 4). Additionally, CT revealed a decrease in intestinal edema, and upper gastrointestinal endoscopy confirmed the disappearance of white-coated spots on the esophagus and stomach mucosa as well as the reduction of mucosal edema (Fig.1 C, D).

The vital signs of the patient were stable, but there were intestinal perforations and severe

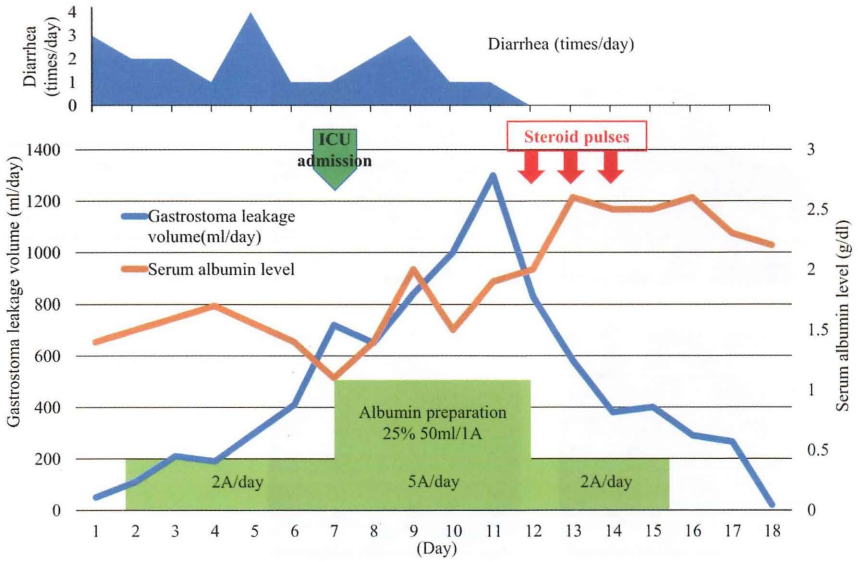

Fig.4. Treatment course (diarrhea, leakage, and serum albumin levels)
Daily total amount of leakage around the gastrostoma dramatically decreased after the pulse steroid therapy, and diarrhea improved. Serum albumin levels were easily controlled by the pulse steroid therapy.

renal dysfunction. Although the patient was in this condition, he was discharged and moved to home care due to the strong intention of his family. He died at home 2 weeks after discharge (1 year and 3 months after the initial diagnosis).

Discussion

Since the treatment for irAEs of the upper gastrointestinal tract has seldom been reported, there are no published treatment guidelines for them. Therefore, we referred to the treatment guidelines for colitis irAEs. According to these guidelines, for Grade 3–4 irAEs, methylprednisolone 1–2 mg/kg should be administered. If improvement is not observed in 3–5 days, further immunosuppressants such as infliximab should be considered [5,6]. In our case, the patient was in a very severe condition and would have died if no progress was seen in 3–5 days. For these reasons, we thought that strong immunosuppressive therapy should be immediately employed. Infliximab was not available because it was not allowed in patients with intestinal perforation. However, some reports have suggested that the pulse steroid therapy was effective for treating hepatitis, hypophysitis, encephalitis and giant cell arteritis caused by irAEs [7-9]. Based on the existing literature, pulse steroid therapy was selected.

After the pulse steroid therapy, the amount of leakage from the gastrostoma decreased dramatically. However, we were unable to evaluate the effect of the treatment on the intestinal perforation because the family did not desire any further examination or treatment.

Despite various treatments, recurrence and metastasis were often observed. However, CT after chemotherapy with paclitaxel and cetuximab showed shrinkage of lung metastases (Fig.2,5). Chemotherapy after immunotherapy has been reported to be effective for squamous cell carcinoma of the head and neck [10]. It has been also shown that the response rate to immunotherapy is greater in patients who develop irAEs [11-13]. These reports are consistent with the present course. We considered the possibility that chemotherapy after immunotherapy might increase the risk of developing irAEs, but there were no reports in the literature that indicated this pos-

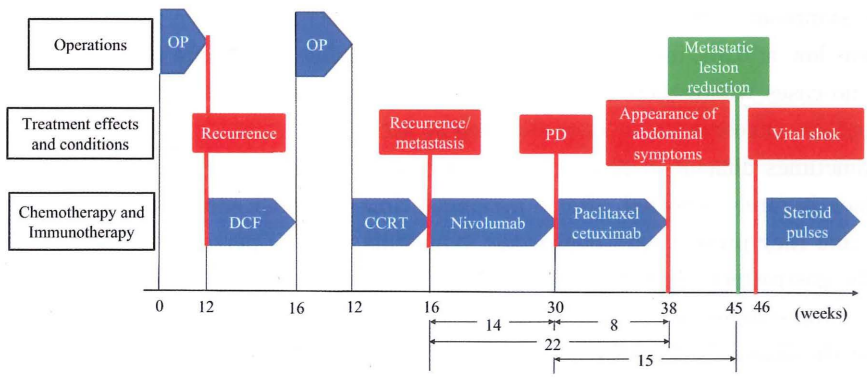

Fig.5. Treatment course by surgery, chemotherapy, and immunotherapy
Although the patient underwent various therapies, recurrence and metastasis were often observed. However, the lung metastasis was clearly reduced 15 weeks after discontinuation of nivolumab and 7 weeks after discontinuation of paclitaxel and cetuximab. DCF: docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and 5-FU 750 mg/m^2 CCRT: concurrent chemoradiotherapy PD: progressive disease

sibility. Although the truth of the matter is unclear, it is important to understand whether irAEs are more likely to be caused by chemotherapy after immunotherapy so that more effective treatment with better response rates can be continued.

CheckMate-017 and CheckMate-057 reported that the median onset time of gastrointestinal irAEs caused by nivolumab is 3–4.7 weeks after the initiation of treatment[14,15]. In our case, the symptoms appeared 5.5 months after the initiation of nivolumab and 2 months after the discontinuation of nivolumab (Fig.5). The irAE of this case might have a much later onset.

Pathological examinations, including immunostaining of biopsy specimens of various organs, have been performed to confirm the diagnosis of irAEs. Uchida et al. reported that the pathological findings of tubulointerstitial nephritis diagnosed as a nivolumab-induced irAE, included extensive infiltration with CD3-positive and CD8-positive T lymphocytes[16]. In addition, in autoimmune pancreatitis and sclerosing cholangitis diagnosed as irAE caused by pembrolizumab, most inflammatory cells were found to be CD8-positive cytotoxic T-cells[17]. Other reports have shown that immunostaining of pathological specimens from hepatitis caused by irAE shows low CD20+/CD3+ and CD4+/CD8+ cell ratios, which is useful for distinguishing irAEs hepatitis from other autoimmune hepatitis [18,19]. It has been reported that it is extremely difficult to distinguish colitis caused by an irAE from ulcerative colitis only by endoscopic findings and hematoxylin and eosin-stained histopathological findings [20], and it is crucial to confirm the histopathological findings including immunostaining for the diagnosis of irAEs.

In the present case, biopsy specimens of duodenal mucosa revealed CD3-, CD4-, and CD8-positive lymphocytic cell infiltration. In particular, the infiltration of CD8-positive lymphocytic cells known as cytotoxic T-cells was so prominent that they infiltrated the crypt glands. In contrast, CD20-positive B lymphocytes were rarely observed. These results indicated that nivolumab caused strong cytotoxic inflammation in the upper gastrointestinal mucosa. There is no report of an upper gastrointestinal irAE showing these immunostaining findings, so this case is considered worthy of report.

In a retrospective study of suspected gastrointestinal irAEs caused by anti-PD-1 antibodies, the actual incidence of gastrointestinal irAEs was estimated to be 1.5%. Diarrhea is generally the main symptom, with an incidence of 1.2%. The incidence of upper gastrointestinal inflammation was low at 0.3%, including gastric ulcer at 0.2% and necrotizing gastritis at 0.15% [21]. In addition, no cases where there have been abnormal findings in the duodenal mucosa on upper gastrointestinal endoscopy have been reported so far.

It is sometimes difficult to diagnose irAEs because they occur in the upper gastrointestinal tract, which is rarely reported, after a prolonged time since ICI administration, as in the present case, and they present with nonspecific symptoms, such as persistent massive fluid leakage around the gastrostoma. In ICI-treated patients, when symptoms are nonspecific and persistent, a biopsy of the symptomatic organs and pathological examination including immunostaining are helpful for the diagnosis of irAEs.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Author's contributions

SI, HO, SOt, and HU participated in the conception and design of the case report, analyzed and interpreted the data and wrote the manuscript. SI, HO, HU, and SOk evaluated the patient and participated in therapy. TK and HM supervised the study and critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Nara City Hospital on January 19, 2022 (approval number: 21-43). Written informed consent was obtained from patient's family member.

Patient consent for publication

The patient's family member provided written consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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