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【 CASE REPORT 】

A Durable Response after the Discontinuation of Nivolumab in an Advanced Gastric Cancer Patient

Yukino Yatsuda[1], Suguru Hirose[1], Yoshimi Ito[1], Tsubasa Onoda[1], Yutaro Sugiyama[1], Miho Nagafuchi[1], Hirosumi Suzuki[1], Yusuke Niisato[1], Yoshitaka Tange[1], Takafumi Ikeda[1], Takeshi Yamada[1], Yoshiyuki Yamamoto[1], Mariko Ohyama Osawa[2], Noriaki Sakamoto[3], Toshikazu Moriwaki[1] and Yuji Mizokami[1]

Abstract:
A durable response after the discontinuation of immune checkpoint-inhibitor therapy has previously been reported in several cancers. We herein describe a patient with gastric cancer who maintained a durable response after the discontinuation of nivolumab. A 65-year-old man was treated with nivolumab as a sixth-line therapy for recurrent gastric cancer. After four cycles of nivolumab therapy, he showed a partial response. But the treatment was discontinued when two immune-related adverse events occurred after six cycles. Disease regression was sustained for approximately 2 years, without the re-administration of nivolumab. The characteristics leading to such responses are unclear, and further studies are warranted in this regard.

Key words: gastric cancer, nivolumab, durable response, immune checkpoint inhibitor, immune-related adverse event, PD-1

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Introduction

Nivolumab, a monoclonal antibody targeting programmed cell death-1 (PD-1), has been shown to provide remarkable efficacy in the treatment of patients with various kinds of malignant tumors and it is approved for the treatment of several cancers, including melanoma (1), non-small cell lung cancer (NSCLC) (2), renal cell carcinoma (RCC) (3), squamous cell carcinoma of the head and neck (4), and Hodgkin's lymphoma (5). The ATTRACTION-2 study was conducted to investigate the efficacy and safety of nivolumab for heavily pretreated advanced gastric cancer (AGC) patients (6). This randomized, double-blind, placebo-controlled phase 3 trial showed the superiority of nivolumab over a placebo, with an objective response rate of 11.2% [95% confidence interval (CI): 7.7-15.6], a median progression-free survival (PFS) of 1.61 months (95% CI: 1.54-2.30), and a median overall survival (OS) of 5.26 months (95% CI: 4.60- 6.37). Based on the results of this study, nivolumab was approved for AGC as either a third- or later-line treatment, and it has been recently recognized as a standard chemotherapeutic regimen in Japan.

Unlike in the case of conventional cytotoxic anticancer drugs or molecular targeted drugs, the blockade of the PD-1 pathway confers an adaptive memory immune response that resets the equilibrium between the tumor and host immune responses, thus indicating its potential to sustain an antitumor response even after treatment cessation (7). Recent studies have reported cases wherein a durable response was observed even after the discontinuation of therapy with immune checkpoint inhibitors (ICIs), including nivolumab, in melanoma, NSCLC, and RCC (8-10), but no such studies have so far been reported in patients with AGC.

Thus, in this study, we report a rare case of an AGC patient who maintained a durable response for approximately 2

[1]Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Japan, [2]Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba, Japan and [3]Department of Diagnostic Pathology, Faculty of Medicine, University of Tsukuba, Japan
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Correspondence to Dr. Toshikazu Moriwaki, tmoriwak@md.tsukuba.ac.jp

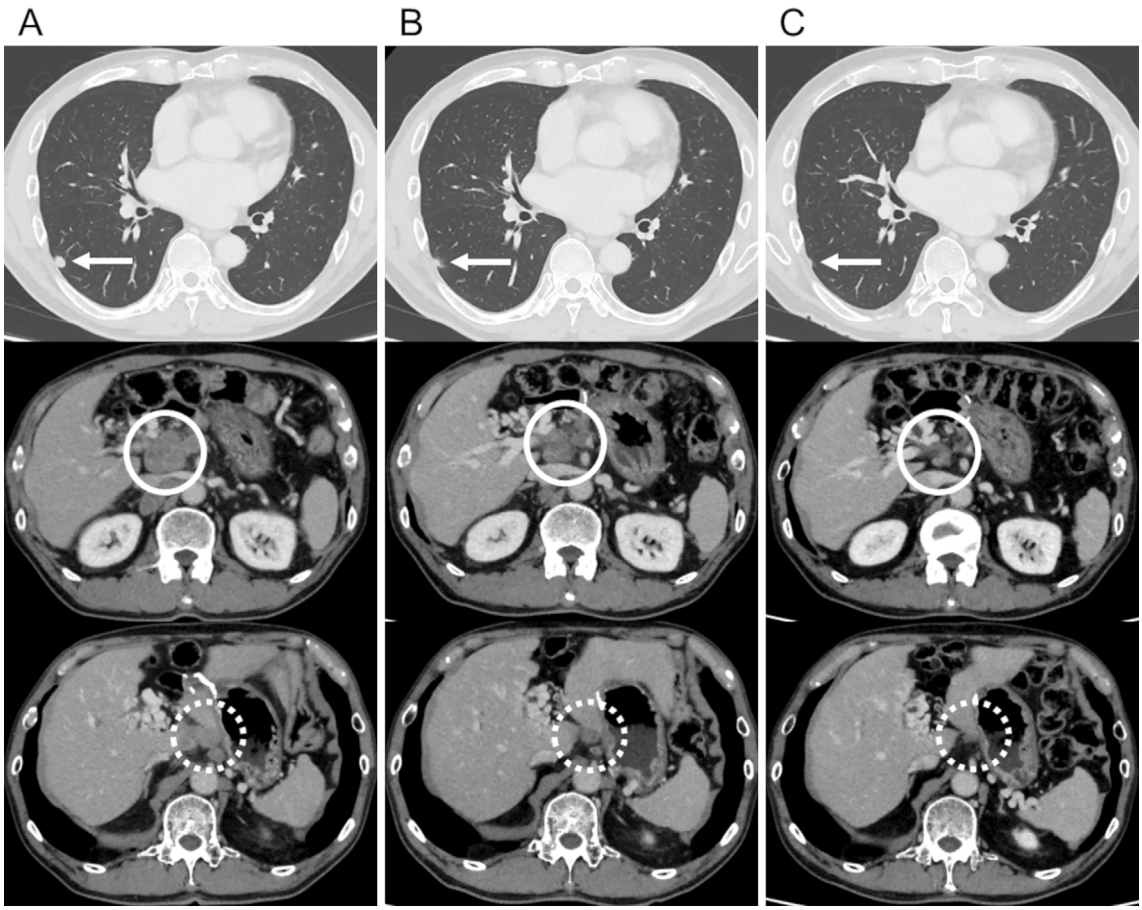

Figure 1. **(A) Abdominal computed tomography images before the commencement of nivolumab treatment. Solitary lung metastasis (arrow), portal tumor thrombus (solid circle), and multiple lymph node metastases (dotted circle) were observed. (B) After four cycles of nivolumab (approximately 2 months after start of nivolumab), the metastatic lesions shrank to 61.2% of the original size (before nivolumab treatment). (C) Twenty-three months after the discontinuation of nivolumab, the metastatic lesions further shrank to 39.1% of the original size (before nivolumab treatment).**

years after the discontinuation of nivolumab due to immune-related adverse events (irAEs).

Case Report

The patient was a 65-year-old man who had been diagnosed with gastric cancer and had undergone total gastrectomy with D2 dissection 7.5 years previously, namely in August 2010. The pathological diagnosis was of a moderately differentiated HER2-negative, pT1N1, pStage IB adenocarcinoma. Six months postoperatively, a solitary liver metastasis was discovered. He then received S-1 treatment as palliative chemotherapy 7 years perviously in March 2011, following which he received nab-paclitaxel alone from May 2013, irinotecan alone from February 2016, capecitabine plus oxaliplatin from June 2016, and ramucirumab alone from February 2017. The disappearance of liver metastasis was observed after the administration of nab-paclitaxel alone. However, treatment with S-1, irinotecan, and ramucirumab was considered to be a failure owing to multiple abdominal lymph node metastases, portal tumor thrombus, and solitary lung metastasis, respectively (Fig. 1A).

Since he exhibited an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, he began to receive nivolumab as sixth-line therapy from March 2018. The laboratory data showed no abnormal findings (Table). The carcinoembryonic antigen and carbohydrate antigen 19-9 levels were within the normal range, which were similar to his preoperative levels. The patient's clinical course during nivolumab treatment is shown in Fig. 2. No adverse events were observed during the first five cycles of nivolumab therapy. However, after the sixth cycle, 15 weeks after the initial treatment, he was hospitalized for severe fatigue (grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0). During hospitalization, he exhibited ECOG PS 3. Physical examination revealed that his body temperature was 36.8℃, blood pressure was 81/48 mmHg, pulse rate was 88/min, and oxygen saturation was 99% on room air. No other abnormal findings were identified. A serum examination revealed a decreased level of thyroid-stimulating hormone (TSH) and increased levels of free triiodothyronine and free thyroxine (T4) compared with the levels before nivolumab initiation (Table).

Table. **Laboratory Data.**

		Reference range	Before nivolumab	After 6 cycles of nivolumab
White blood cells	/μL	4,000-9,000	3,500	3,400
Neutrophils	%	45-55	47.8	47.7
Lymophocyte	%	25-45	36.9	36.5
Hemoglobin	g/dL	14-18	14.4	13.8
Platelets	/μL	15-35×10^4	11.3×10^4	19.9×10^4
Lactate dehydrogenase	U/I	106-211	155	249
Total bilirubin	mg/dL	0.3-1.2	1.2	1.1
Sodium	mEq/L	135-147	141	138
Potassium	mEq/L	3.6-5.0	4.0	4.7
Chloride	mEq/L	98-108	105	101
Calcium	mg/dL	8.6-10.1	8.7	9.4
Urea nitrogen	mg/dL	8-20	10.7	16.7
Creatinine	mg/dL	0.61-1.04	0.95	1.00
C-reactive protein	mg/dL	0-0.2	<0.03	0.46
Casual blood glucose	mg/dL	70-199	–	192
Hemoglobin A1c	%	4.6-6.2	5.5	5.4
CA19-9	U/mL	<37.0	8.6	–
CEA	ng/mL	<5.0	2.3	–
TSH	μU/mL	0.5-5.0	4.16	0.021
FT4	ng/dL	0.9-1.7	0.99	2.48
FT3	pg/mL	2.3-4.3	2.6	7.9
ACTH	pg/mL	7.2-63.3	78.6	3.5
Cortisol	μg/dL	7.07-19.6	14.6	0.2
GH	ng/mL	0.0-2.0	–	1.2
LH	mIU/mL	0.79-5.72	–	6.1
FSH	mIU/mL	2.00-8.30	–	12.8
Prolactin	ng/mL	4.29-13.69	–	9.7

ACTH: adrenocorticotropic hormone, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, FSH: follicle stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, GH: growth hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone

The patient tested negative for thyroid autoantibodies. In addition, there was a decrease in the levels of adrenocorticotropic hormone (ACTH) and cortisol. A stimulation test revealed a minor impact of corticotropin-releasing hormone loading on the ACTH and cortisol levels, while growth hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, and TSH showed sufficient responses according to the corresponding stimulation tests. The ultrasound findings of the thyroid and magnetic resonance imaging findings of the pituitary gland showed no abnormalities. Consequently, he was diagnosed to have grade 3 isolated ACTH deficiency with secondary adrenal insufficiency and nivolumab-related grade 3 destructive thyroiditis. Nivolumab therapy was discontinued and prednisolone was supplemented at a starting dose of 15 mg/day for adrenal insufficiency. The patient's fatigue was alleviated within a few days, following which the prednisolone dose was tapered. His serum cortisol level returned to normal, whereas ACTH deficiency persisted. Prednisolone was maintained at a dosage of 5 mg/day since day 37, and no relapse was noted thereafter. The free T4 level decreased on day 23, confirming the hypothyroidism phase of destructive thyroiditis. Levothyroxine (25 μg/day) was administrated until the free T4 level recovered on day 95, and no relapse occurred thereafter.

After four cycles of nivolumab (approximately 2 months after the start of nivolumab therapy), all metastatic lesions shrank to around 61.2% of the size before nivolumab treatment (Fig. 1B). We determined to observe his course without the re-administration of nivolumab even after the improvement of irAEs. The metastatic lesions further decreased in size after the discontinuation of nivolumab, and the effect was sustained for 23 months after nivolumab initiation (final size, 39.1% of that before nivolumab treatment) (Fig. 1C); the tumor markers were within the normal ranges.

Discussion

Recently, a durable response after the discontinuation of ICIs in patients with residual disease has been reported for other kinds of cancers (8-10). It has previously been reported that PD-1/PD-L1 blockade rescued "exhausted" T cells, leading to the activation of T-cell effectors and transition to memory cells (7). The level of PD-1 occupancy on circulating T cells was shown to persist much longer than the serum half-life of the PD-1 antibodies (11, 12). This might mean that there is no need to perform continuous

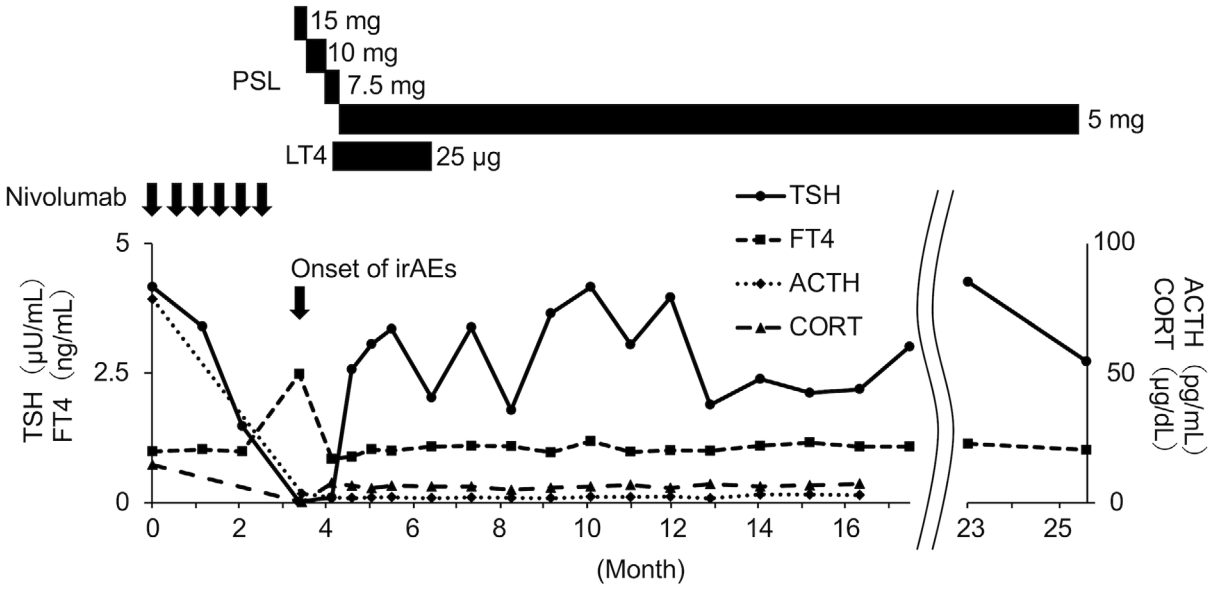

Figure 2. **The patient's clinical course during nivolumab treatment. ACTH: adrenocorticotropic hormone, CORT: cortisol, FT4: free thyroxine, LT4: levothyroxine, PSL: prednisolone, TSH: thyroid stimulating hormone**

treatment with ICIs. In fact, our patient showed that the metastatic lesions further decreased after the discontinuation of nivolumab.

Several predictive markers of an effective response to ICIs have been previously proposed for many cancers including AGC, such as better ECOG PS, no liver or lung metastases, a higher peripheral lymphocyte count, a lower neutrophil-to-lymphocyte ratio, a higher tumor PD-L1 expression, and a high degree of microsatellite instability (6, 13-17). However, there have been a limited number of case reviews about the predictive markers for a durable clinical benefit after the discontinuation of ICIs, namely only in melanoma and RCC cases (8, 10, 18). In the KEYNOTE-001 study on pembrolizumab in patients with melanoma, 61 of 67 patients (91.0%), who were followed up after pembrolizumab discontinuation after a complete response (CR), achieved a disease-free survival of 24 months (18). It was suggested that the patients with CR were more likely to achieve a durable response. A univariate analysis revealed that high CR rates were associated with a target tumor size between 1 and 5 cm and PD-L1-positive tumors (≥1% staining in tumor cells and mononuclear inflammatory cells) (18). A retrospective cohort study on melanoma patients showed that the risk of disease progression following treatment discontinuation was significantly associated with the overall response and it was lower in patients with CR (19). However, none of these conditions were seen in our patient (no CR, unknown tumor PD-L1 status, and target tumor size: 7.7 cm; data not shown). In addition, our patient did not exhibit any microsatellite instability (data not shown). Since the Epstein-Barr virus (EBV)-positive status might be a marker of an effective response to ICIs in AGC (20, 21), we performed EBV-encoded small RNA *in situ* hybridization on the primary tumor, which showed positivity in the nuclei of the tumor cells (Fig. 3). This result was consistent with that reported in previous reports (20, 21). However, there are no reports on the predictive markers for a durable clinical benefit after the discontinuation of ICIs in AGC, and further study in many similar cases will be needed to clarify this, regardless of the distinctive features seen in our patient.

Recent studies have shown that the development of irAE was associated with a clinical benefit in several cancers, including AGC (22-28). In NSCLC patients, in whom irAEs developed within 2 weeks from the start of nivolumab treatment (25), in whom more than two irAEs were reported (26), or in whom either endocrine irAEs or skin irAEs (28), a more pronounced benefit was observed. In melanoma cases, the occurrence of vitiligo as an irAE was associated with a clinical benefit (23, 29, 30), while endocrine irAE was not (23). In our patient, although the time to irAE occurrence was 15 weeks, which was longer than 2 weeks, two irAEs were detected, both of which were endocrine irAEs. The association between the types of irAEs and the clinical outcomes in different cancer types is still unclear.

ICIs induce multiple-organ irAEs via immune system overactivation (31). Two irAEs were observed in our patient. The incidence of endocrine irAEs varies depending on the agent, and nivolumab induces thyroid disorders in approximately 10% of such patients and hypophysitis in less than 1% of such patients (32, 33). A patient often shows the development of multiple irAEs, but the common patterns of irAEs have been rarely reported. Although the pathogenic mechanism of ICI-triggered hypophysitis is unknown, the characteristic symptoms and imaging findings resemble those of autoimmune hypophysitis (34), which was also seen in our patient. The current guidelines suggest corticosteroid therapy and the replacement of deficient hormones to man-

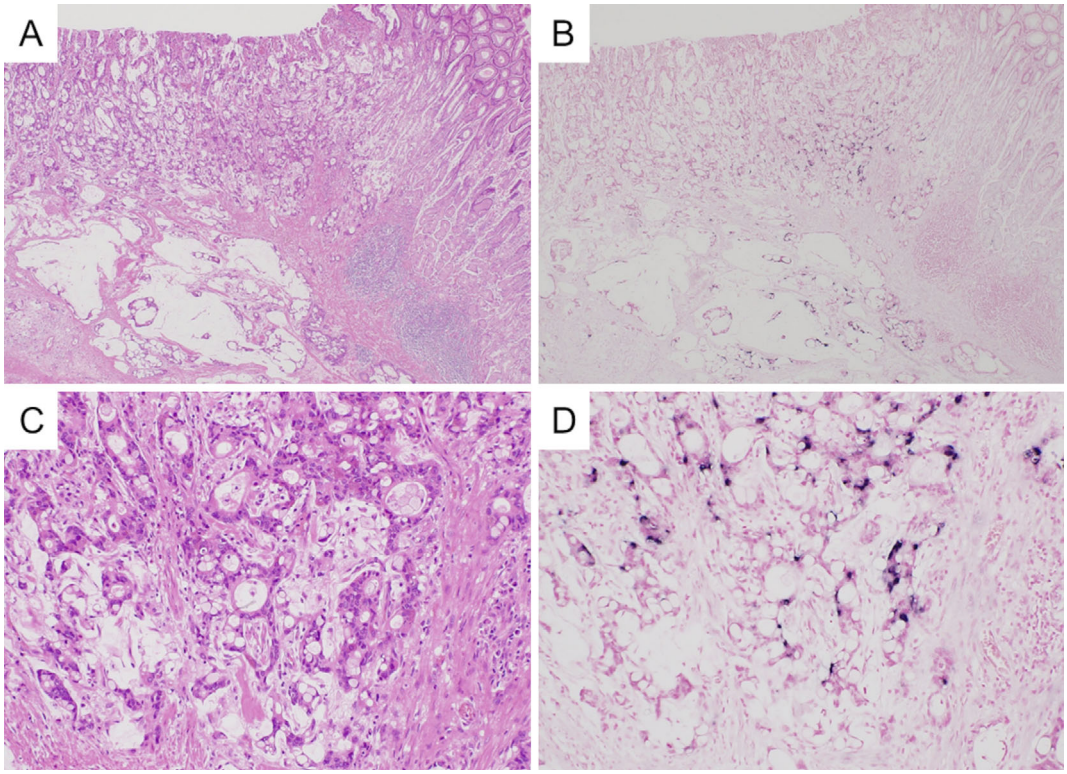

Figure 3. **Hematoxylin and Eosin staining (A magnification 40×, C magnification 200×) and Epstein-Barr virus-encoded small RNA *in situ* hybridization (B magnification 40×, D magnification 200×) in the resected primary tumor.**

age endocrine irAEs (35), and long-term hormonal replacement is indicated for ACTH deficiency secondary to hypophysitis (36), which was also effective in our patient.

Recent studies have reported that recurrence of the same or different irAEs was observed in 18-52% of patients who received ICI re-administration (37-39), and these were milder than the initial events (38-40). A large-scale observational study using data from the World Health Organization database reported that colitis, hepatitis, and pneumonitis are associated with a higher recurrence rate, whereas adrenal events are associated with a lower recurrence rate compared with other irAEs (40). The efficacy of ICI re-administration is not yet established. A large retrospective analysis of NSCLC patients who were discontinued nivolumab therapy for any reason showed that OS in patients who received ICI re-administration was significantly better than that in patients who received chemotherapy only after nivolumab, in a sub-group analysis among the patients who initially received nivolumab therapy for more than 3 months (41). On the other hand, a retrospective cohort study on ICI re-administration in patients with solid tumors after the occurrence of an initial grade 2 or higher irAE showed that PFS in the re-administered patients was not better than that in the non-re-administered patients (38). If recurrence is observed in our case, then we will consider the re-administration of ICI while carefully monitoring irAEs.

In conclusion, we treated a patient with AGC who maintained a durable response for approximately 2 years after discontinuation of nivolumab. To the best of our knowledge, this is the first report to describe a durable clinical benefit after the discontinuation of nivolumab in gastric cancer. Further studies are necessary to elucidate the mechanism and the predictive markers of a durable clinical benefit after ICI discontinuation. The risks and benefits of ICI re-administration should be considered on the basis of the type of initial irAE.

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

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