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Case Report

A Case of Long-Term Survival with Recurrent Liver Metastases from Gastric Cancer Treated with Nivolumab

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Keywords
Nivolumab · Gastric cancer · Liver metastases · Long survival

Abstract
Introduction: Improvements in overall survival from advanced gastric cancer have recently been reported with nivolumab. However, few reports have described long-term survival after discontinuing treatment. ***Case Presentation:*** A 67-year-old man diagnosed with advanced gastric cancer and abdominal aortic aneurysm initially underwent distal gastrectomy with D2 dissection. Histological examination revealed tub2 and T2N1M0 stage IIA. One month later, endovascular aneurysm repair was performed. Six weeks after gastrectomy, adjuvant chemotherapy with S-1 was started. Six months later, liver metastases were identified and liver segments S1 and S7 were resected. S-1 and oxaliplatin were added postoperatively, but multiple liver metastases recurred. Paclitaxel and ramucirumab, irinotecan, and docetaxel were administered. Liver metastases showed a temporary reduction in size, then enlarged again. Nivolumab was therefore administered and the liver metastases showed a significant reduction in size. The interval between doses gradually increased due to persistent general fatigue. At 28 months after starting nivolumab therapy, bronchitis and adrenal insufficiency appeared, so treatment was discontinued. As of 3.5 years after cessation of nivolumab immunotherapy, tumor regression continued to be maintained. The patient remains alive as of 8 years after recurrence of liver metastases. ***Conclusion:*** We encountered a case in which the patient received nivolumab therapy for recurrent liver metastases from gastric cancer and survived long term after discontinuing treatment.

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Introduction

Nivolumab has been used to treat advanced gastric cancer and improvements in overall survival (OS) have been reported. A 3-year survival rate of 35.5% was reported among responders who achieved complete response (CR) or partial response (PR) in the long-term results of the ATTRACTION-2 study [1–3]. Moreover, that report suggested a survival benefit from continuing treatment beyond progression. Following studies that demonstrated the efficacy of nivolumab against advanced gastric cancer, various case reports have described nivolumab as very effective [4–12]. However, ATTRACTION-2 included only 3 cases with CR lasting more than 3 years. In addition, few reports have described long-term follow-up after discontinuing treatment. We encountered a patient with multiple recurrences of liver metastases after gastric cancer surgery and liver resection who was treated with nivolumab and maintained CR for 3.5 years after discontinuation due to immune-related adverse events (irAEs). We report this case with reference to the literature.

Case Presentation

The patient was a 67-year-old man. Esophagogastroduodenoscopy revealed Borrmann type 3 advanced gastric cancer at the pyloric region and abdominal ultrasonography revealed abdominal aortic aneurysm. The patient initially underwent distal gastrectomy and D2 dissection for Borrmann type 3 advanced gastric cancer. One month later, endovascular aortic repair was performed for the abdominal aortic aneurysm. The size of the gastric tumor was 40 × 27 mm, and the pathological report identified tubular adenocarcinoma: tub2 and T2N1M0 stage IIA. Six weeks after gastrectomy, postoperative adjuvant chemotherapy was started with oral TS-1 (120 mg/body; days 1–14 every 3 weeks). Six months later, abdominopelvic computed tomography (CT) showed multiple tumors in liver segments S1 and S7 and partial resection of the caudate lobe and posterior segment was performed. The pathological report showed metastatic adenocarcinoma from gastric cancer and HER-2 positive.

Eight courses of S-1 (120 mg/body; days 1–14 every 3 weeks) and oxaliplatin (80 mg/m^2 every 3 weeks) were added after liver resection, but 7 months later, the tumor recurred with multiple liver metastases. Nine courses of paclitaxel (80 mg/m^2; days 1, 8, and 15) and ramucirumab (8 mg/kg; days 1 and 15) therapy, three courses of irinotecan (140 mg/m^2 every 2 weeks), and four courses of docetaxel (50 mg/m^2 every 3 weeks) were added sequentially. Liver metastases temporarily reduced in size, but the tumor enlarged again (Fig. 1a). Nivolumab (3 mg/kg every 2 weeks) was therefore started and the liver metastases displayed a reduction in size after 2 months (Fig. 1b). Administration of nivolumab was continued and the tumor shrank further (Fig. 1c), but the patient suffered from general malaise. The dose interval of nivolumab was gradually increased to every 4, 6, and 8 weeks while liver metastases were monitored by CT.

After 28 months of nivolumab administration, the patient developed cough due to bronchitis and malaise had worsened, so nivolumab was discontinued (Fig. 2a). Two months after discontinuing nivolumab, bronchitis symptoms had improved, but malaise had worsened, blood pressure had decreased, and adrenocorticotropic hormone and cortisol levels had declined. Adrenal insufficiency was diagnosed and steroid therapy was started with hydrocortisone, leading to improvements in general malaise and gradual recovery of adrenocorticotropic hormone and cortisol levels. Moreover, the metastatic tumors shrank further after discontinuation of nivolumab (Fig. 2b). Nine months after discontinuation of nivolumab, CT showed that the liver metastases had almost disappeared (Fig. 2c). Hydrocortisone

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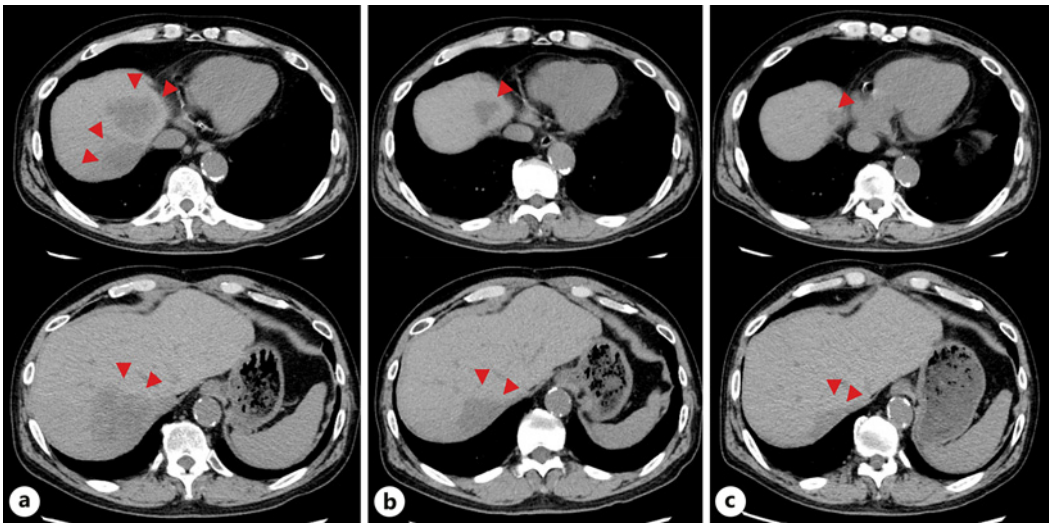

Fig. 1. **a** Before nivolumab therapy, multiple liver metastases are apparent. **b** Two months after nivolumab therapy, the tumor has shrunk. **c** Nine months after nivolumab therapy, the tumor has shrunk further.

administration was tapered off and discontinued after 1.5 years of treatment. Currently, as of 3.5 years after discontinuation of nivolumab and 8 years after recurrence of liver metastases, no radiological evidence of recurrence has been identified (Fig. 3).

Discussion

Immune checkpoint inhibitors (ICIs) have enabled long-term survival in a certain percentage of patients with advanced cancer, which had been extremely difficult using conventional cytotoxic anticancer agents. However, long-term survival was achieved in relatively few cases [3, 13]. Studies have therefore been conducted to further improve response rates. ICIs were initially standard treatment for late-line therapy alone but have since been used in combination with chemotherapeutic agents as first-line treatment to improve response rates. Attempts have also been made to identify the patient populations for whom immunotherapy is effective and suitable. PD-L1 expression, microsatellite instability high, Epstein-Barr virus, and tumor mutational burden may represent biomarkers of gastric cancer response to ICIs [14]. Understanding the tumor microenvironment in gastric cancer progression is also important. Combinations of ICIs and molecularly targeted therapies, vaccine therapy, and chimeric antigen receptor (CAR)-T therapy are being investigated in terms of the involvement of immunocompetent cells in the progression of gastric cancer [15]. An antibody-drug conjugate of trastuzumab and deruxtecan was used in HER2-positive gastric cancer and was recommended for the treatment of HER2-positive gastric cancer due to improved OS [16]. In genome-based analyses of gastric cancer, drugs targeting the DNA damage response are being developed. Combination studies are underway for DNA damage response-targeted agents with various drugs, including chemotherapy, ICIs, and anti-VEGF monoclonal antibodies [17]. Other studies have been conducted on sex and prognosis in patients treated with ICIs and their combinations and on the relationship between Eastern Cooperative Oncology Group performance status and improved survival [18, 19].

Various cases of nivolumab being effective against advanced gastric cancer have been reported in recent years [4–12]. Those reports are summarized in Table 1, excluding cases

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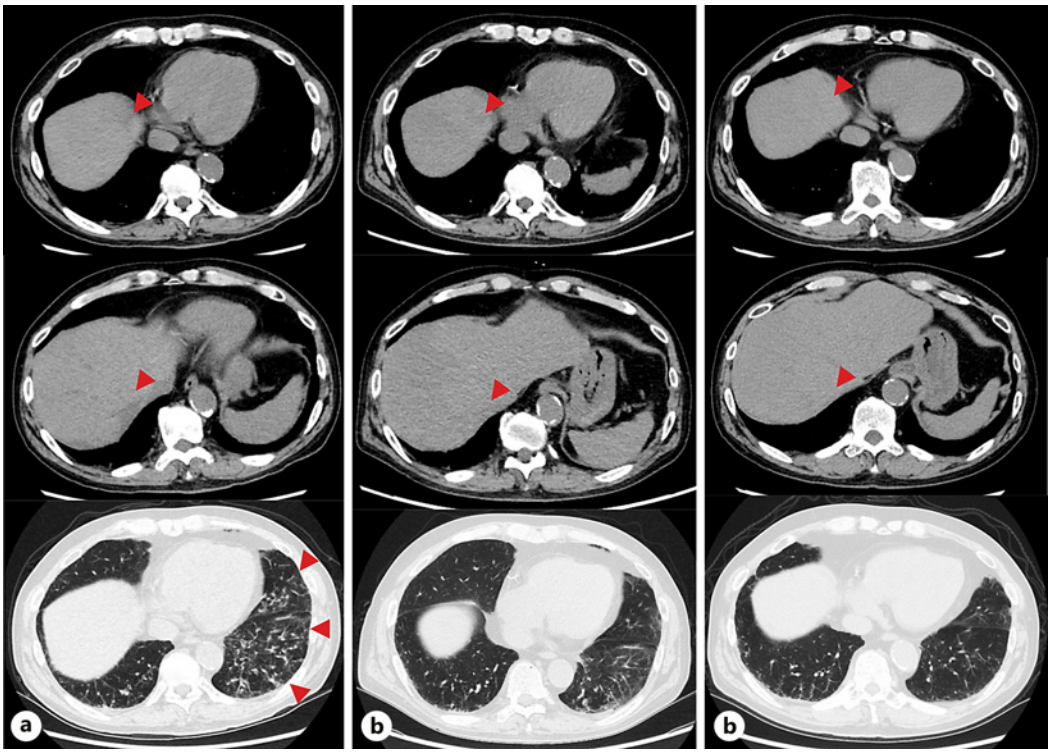

Fig. 2. **a** At the discontinuation of nivolumab therapy, the tumor remains in a shrunken state, but infiltrative shadows are seen in the lung fields. **b** Five months after discontinuation of nivolumab therapy, the tumor has shrunk further. Infiltrative shadows in the lung fields are reduced. **c** Nine months after discontinuation of nivolumab therapy, liver metastases have almost disappeared. Infiltrative shadows in the lung fields show further improvement.

converted to surgery after successful treatment. Postoperative recurrence occurred in 6 cases and was unresectable in 4 cases. Metastatic sites were the lymph nodes in 6 cases, liver in 3 cases, peritoneum in 4 cases, and lungs in 1 case, showing efficacy regardless of whether primary or metastatic sites were involved. Of the 7 cases in which treatment was discontinued, five were discontinued due to side effects, one was changed to another treatment regimen, and one was discontinued after maintenance of CR. The other 3 patients continued treatment with CR or PR. Maximum duration of nivolumab treatment was 3 years. In cases of Table 1, response was achieved within a short period of time, ranging from 1.5 months to 3 months after the start of nivolumab administration. This suggests that once the immune system is switched on, the effects may be sustained.

Table 2 summarizes the ATTRACTION-2 and CheckMate-032 cases treated with nivolumab alone [1–3, 13]. Most were administered nivolumab as more than third-line therapy, indicating effectiveness can be expected without being affected by previous treatment. Most of Table 1 cases were also third line or higher. The disease control rate was 37–40%, but only 3 CR cases were included, a small number. The average duration of response was 9.53–14.1 months, shorter than the 6–70 months for cases of Table 1. Nivolumab can therefore be used effectively if these successful cases can be selected. However, PD-L1 expression has not been correlated with survival or response rates. In cases of Table 1, both cases in which PD-L1 expression was measured showed negative results and CR. The number of patients with PD-L1 expression in the two studies was also small and should be re-evaluated in studies with larger cohorts in the future.

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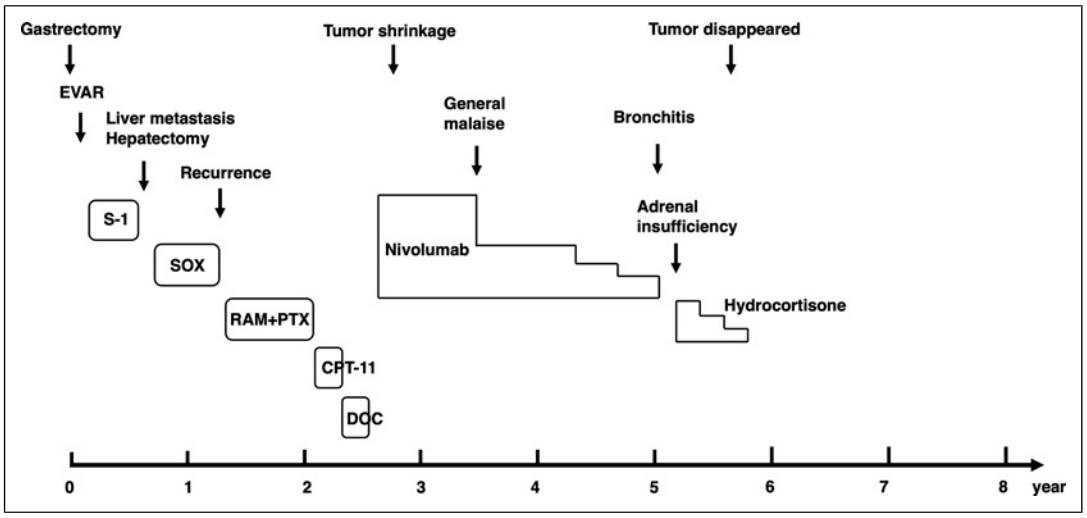

Fig. 3. Clinical course. EVAR: endovascular aneurysm repair; S-1 (120 mg/body; days 1–14 every 3 weeks); SOX: S-1 (120 mg/body; days 1–14 every 3 weeks) and oxaliplatin (80 mg/m^2 every 3 weeks); RAM + PTX: ramucirumab (8 mg/kg; days 1, 15) and paclitaxel (80 mg/m^2; days 1, 8, 15); CPT-11: irinotecan (140 mg/m^2 every 2 weeks); DOC: docetaxel (50 mg/m^2 every 3 weeks); nivolumab was started at 3 mg/kg every 2 weeks and the dose interval of nivolumab was gradually increased to every 4, 6, and 8 weeks; hydrocortisone was started at 15 mg and then tapered off.

ATTRACTION-2 showed a 43% incidence of treatment-related adverse events (TRAEs), 10% with grade 3 or 4 TRAEs, and 2% with discontinuation of treatment due to TRAEs [1]. CheckMate-032 showed a 69% incidence of TRAEs, 17% with grade 3 or 4, and 3% with discontinuation due to TRAEs [13]. In cases of Table 1, administration of nivolumab was discontinued due to irAEs in half of those cases, more frequent than in the above two studies. Patients who responded to nivolumab may have been more likely to experience side effects because of the longer duration of treatment than those who did not respond. In the cases in Table 1, side effects appeared after 3–10 months, which is not as long as the survival of the placebo group in ATTRACTION-2. Matsuda et al. [20] compared 65 patients with advanced gastric cancer treated with nivolumab with and without irAEs and found that patients with irAEs achieved longer survival even after accounting for these lead-time bias, suggesting irAEs as a factor that influences prognosis. However, the persistence of efficacy after drug discontinuation means that side effects may also occur. In our case, adrenal insufficiency appeared 2 months after discontinuation. Careful management of side effects therefore appears warranted for a certain period after discontinuing administration.

Clear criteria are lacking on when to discontinue nivolumab in cases showing long-term response to this drug. Our case showed the longest response reported to date, with efficacy maintained for 3.5 years after treatment discontinuation. Looking at other cases in Table 1, 1 patient who had received the drug for 3 years maintained CR and discontinuation was considered, but administration was continued due to the lack of clear criteria and based on the wishes of the patient [12]. In another case of CR, the patient was still receiving the drug because of a fear of recurrence after discontinuation [4]. In the end, only 1 patient discontinued treatment after achieving CR, even though no side effects were reported [5]. In our case, after the metastases maintained a reduced size, we considered whether to continue nivolumab administration. As we were concerned about tumor regrowth, we continued treatment with gradually increasing intervals between doses.

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Table 1. Reported cases of advanced gastric cancer in which nivolumab was effective

No	Author, year	Age/ sex	Target lesion	Prior regimens, *n*	HER-2	PD-L1 ≥1%	MSI high	TTR, months	Nivolumab duration, months	Outcome, months	Effect	DOR, months	irAE
1	Namikawa et al. [4] (2018)	77/M	Li	2	NA	NA	NA	2	11	Continuation	CR	11	
2	Kashima et al. [5] (2019)	25/F	LN	1	Positive	Negative	Negative	2	12	Discontinuation (24)	CR	36	
3	Tazawa et al. [6] (2019)	66/F	S, P	3	NA	NA	NA	3	6	Replaced (12)	PR	6	
4	Arigami et al. [7] (2020)	65/M	LN	2	Negative	NA	NA	2	6	Discontinuation (15)	PR	21	DM
5	Doi et al. [8] (2020)	69/F	S, LN, P, Li	2	Negative	NA	Negative	1.5	7.5	Discontinuation (10)	CR	17	Muscle weakness
6	Nakamura et al. [9] (2020)	71/F	S, LN	2	Negative	NA	NA	3	7	Continuation	PR	7	
7	Komo et al. [10] (2021)	70/F	S, LN, P	2	NA	NA	NA	NA	4.5	Discontinuation (14)	CR	21	IP
8	Yatsuda et al. [11] (2021)	65/M	LN, Lu	5	Negative	NA	Negative	2	3	Discontinuation (20)	PR	23	ADH, destructive thyroiditis
9	Takami et al. [12] (2021)	70/F	P	1	Negative	Negative	Negative	3	36	Continuation	CR	36	
10	Our case (2023)	67/M	Li	4	Positive	NA	NA	2	28	Discontinuation (42)	CR	70	ADH, bronchitis

TTR, time to response; DOR, duration of response; irAE, immune-related adverse event; Li, liver; LN, lymph node; S, stomach; P, peritoneum; Lu, lung; NA, not available; CR, complete response; PR, partial response; DM, diabetes mellitus; IP, interstitial pneumonia; ADH, adrenal hypofunction.

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Table 2. Summary of ATTRACTION-2 and CheckMate-032

	ATTRACTION-2 [1–3] (*n* = 330)	CheckMate-032 [13] (*n* = 59)
Prior regimens		
1	0	10
2	69	20
3	137	19
>3	124	10
HER-2	Not available	
Positive		8
Negative		30
Not available		21
PD-L1 ≥1%		
Positive	16 (MOS 5.22 months)	16 (DCR 31%)
Negative	114 (MOS 6.05 months)	26 (DCR 42%)
Not available	200	17
MSI high	Not available	
Positive		7 (DCR 71%)
Negative		18 (DCR 28%)
Not available		34
Overall response	(*n* = 268)*	
CR	3	0
PR	29	4
SD	76	18
PD	124	26
Not evaluated	36	6
DCR	108 (40.3%)	22 (37%)
Median TTR, months	1.61 (1.4~3.0)	1.4 (1.2~2.1)
Median DOR, months	9.53 (6.14~9.82)	14.1 (2.8~14.1)

MOS, median overall survival; DCR, disease control rate; TTR, time to response; DOR, duration of response.
*Sixty two excluded from analysis due to no baseline target lesion.

Administration of nivolumab must be discontinued in cases where adverse reactions occur, and measures for discontinuing nivolumab in cases of CR without adverse reactions are needed in the future. As in the present case, one method would be to taper the dosage while conducting follow-up imaging. A review of lung cancer patients treated with nivolumab may be helpful [21]. In this study, after 1 year of treatment with nivolumab for previously treated advanced lung cancer, OS was better in the continued treatment group compared to the discontinued group. Furthermore, analysis of CR and PR cases also revealed that both progression-free survival and OS were better in the continuous treatment group. In this study, the maximum duration of nivolumab administration was 3 years. In other words, even if nivolumab treatment is successful and results in CR or PR, discontinuation within 1 year is not considered good in terms of prognosis. In addition, considering that nivolumab maintains equilibrium by suppressing tumor growth, if not completely eliminating tumors, the duration of administration should be further extended. Continued accumulation of reports on the long-term prognosis after nivolumab treatment will provide better indications regarding the optimal duration of treatment. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537779).

Conclusion

In this case, nivolumab was discontinued due to irAE, but the tumor subsequently reduced in size and CR was maintained for an extended period. No reports have yet clarified how long treatment should be continued in patients who have been successfully treated with nivolumab.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethics approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

A.H. and S.A. performed the surgery and chemotherapy. Y.F., S.K., and T.A. collected the clinical data. A.H. wrote the manuscript. All authors participated in the preparation of this manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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