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CASE REPORT

# A case of multiple metastatic gastric cancer with primary lesion vanished after administrating nivolumab, and the effect remains even after discontinuance of therapy

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**Abstract**
Nivolumab is one of the immune checkpoint inhibitors available for chemotherapy-resistant gastric cancer. There have been few reports of confirmed prominent shrinkage of the primary tumor and some reports of prolonged antitumor effect after discontinuance of the drug, but it is not universal. A 67-year-old male was admitted to our hospital and diagnosed with metastatic gastric cancer that had spread to the bilateral lobe of the liver, distant lymph nodes, and peritoneum. He received five courses of S-1 plus oxaliplatin, followed by three courses of ramucirumab plus paclitaxel leading to disease progression. Then, the patient was administered nivolumab as third-line therapy. Tumor size was markedly reduced after three courses, esophagogastroduodenoscopy (EGD) revealed scar formation on the lower gastric corpus after seven courses, and biopsy specimen showed no malignancy. When a slight lower limb muscle weakness manifested, possibly an immune-related adverse event (irAE) after 15 courses, we stopped administration of nivolumab. The patient has survived for 26 months since his first visit, and elimination of the primary tumor and ascites with noted shrinkage of liver and lymph node metastases have followed for more than 10 months since discontinuance of nivolumab.

**Keywords** Gastric cancer · Nivolumab · Complete response · Prolonged effect · Double cancer

## Introduction

Nivolumab was approved for gastric cancer in Japan in 2017. Its disease control rate (DCR) against unresectable gastric cancer was 40.3% (0% of complete response, 11% of partial response, 29% of stable response) in ATTRACTION-2 trial [1]. Two-year additional update data showed three patients (1.1%) with complete response (CR) [2]. Shrinkage of gastric cancer is rarely reported in spite of its fairly high DCR. Antitumor effect after discontinuation of nivolumab has been observed in various cancers [3–5]. But it is unclear when to stop administrating nivolumab if CR was obtained. In addition, it is indistinct how long the antitumor effect continues after discontinuation. Herein, we reported a case of multiple metastatic gastric cancer with primary lesion that vanished after administrating nivolumab, and the effect remains even after discontinuance of the therapy.

## Case presentation

A 67-year-old male admitted to our hospital complaining of nausea, epigastralgia for 2 month, and melena for 1 month. Blood examination showed anemia, high level of hepatobiliary enzymes and carcinoembryonic antigen (CEA). Esophagogastroduodenoscopy (EGD) revealed type 3 tumor on the lower gastric corpus and pathologic examination of a biopsy specimen showed poorly differentiated adenocarcinoma including signet ring cell (Fig. 1a). Both human epidermal growth factor 2 (HER2) and microsatellite instability (MSI) status were negative. Epstein-Barr virus (EBV)-encoded RNA hybridization

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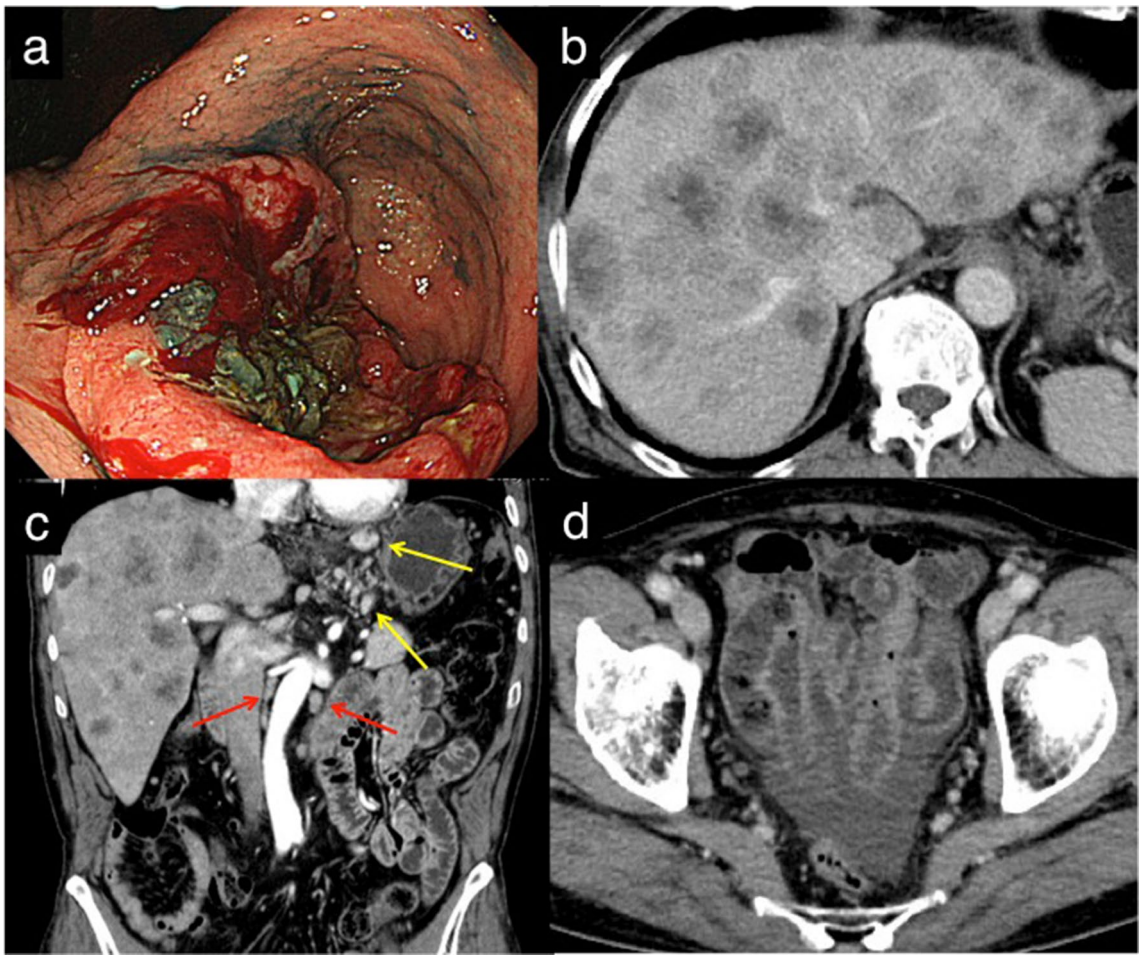


**Fig. 1** Initial examination findings. **a** Type 3 advanced tumor on the lower gastric corpus. **b** Multiple liver metastases in the bilateral lobe. **c** Perigastric lymph node metastases (yellow arrows) and para-aortic lymph nodes metastases (red arrows). **d** Ascites at the floor of the pelvic

showed an undeterminable stained image. Computed tomography (CT) revealed multiple liver metastases, multiple lymph nodes metastases including the para-aortic region, and peritoneum metastases with ascites (Fig. 1b–d). Clinical diagnosis was cT4a, cN3, cM1, cStageIVB according to Japanese Classification of Gastric Carcinoma, the 15th Edition. He received chemotherapy with S-1 plus oxaliplatin (SOX) as the first-line pharmacotherapy and melena disappeared after two courses. He also became able to take a meal without discomfort. EGD and CT showed shrinkage of primary lesion and lymph nodes, disappearance of ascites, and evident improvement of liver metastases (Figs. 2a, 3a). Nevertheless, EGD and CT revealed regrowth of primary lesion, lymph nodes metastases, and recurrence of ascites, though liver metastases remained suppressed after five courses (Figs. 2b, 3b). At that time, EGD revealed another early stage gastric cancer on the proximal side of the main lesion and biopsy specimen was diagnosed as well differentiated tubular adenocarcinoma which is different from the main lesion (Fig. 4a). Though chemotherapy was changed to ramucirumab plus paclitaxel (RAM+PTX) as the second-line pharmacotherapy after progression, CT showed enlargement of metastatic lymph nodes after three courses. Nivolumab was introduced as the third-line treatment. CT demonstrated shrinkage of primary lesion and lymph node metastases and disappearance of ascites after three courses. And after seven courses, EGD revealed scar lesion on the lower gastric corpus where the main lesion was located, and biopsy specimen was filtration of neutrophils, plasma cells, and lymphocytes, but no tumor cells (Fig. 2c). There were some small low-density lesions in the liver on the CT (Fig. 3c). When a slight lower limb muscle weakness manifested after 15 courses, we suspected immune-related adverse event (irAE) and stopped administration of nivolumab. Though EGD showed no recurrence of main lesion after the discontinuance, another early gastric cancer remained stable. Endoscopic submucosal dissection (ESD) for the lesion was completed and pathological finding revealed intramucosal tumor (Fig. 4b). EBV-encoded RNA hybridization showed a negative staining. We have been carefully following up by tumor marker, CT, positron emission tomography CT (PET-CT), and EGD.

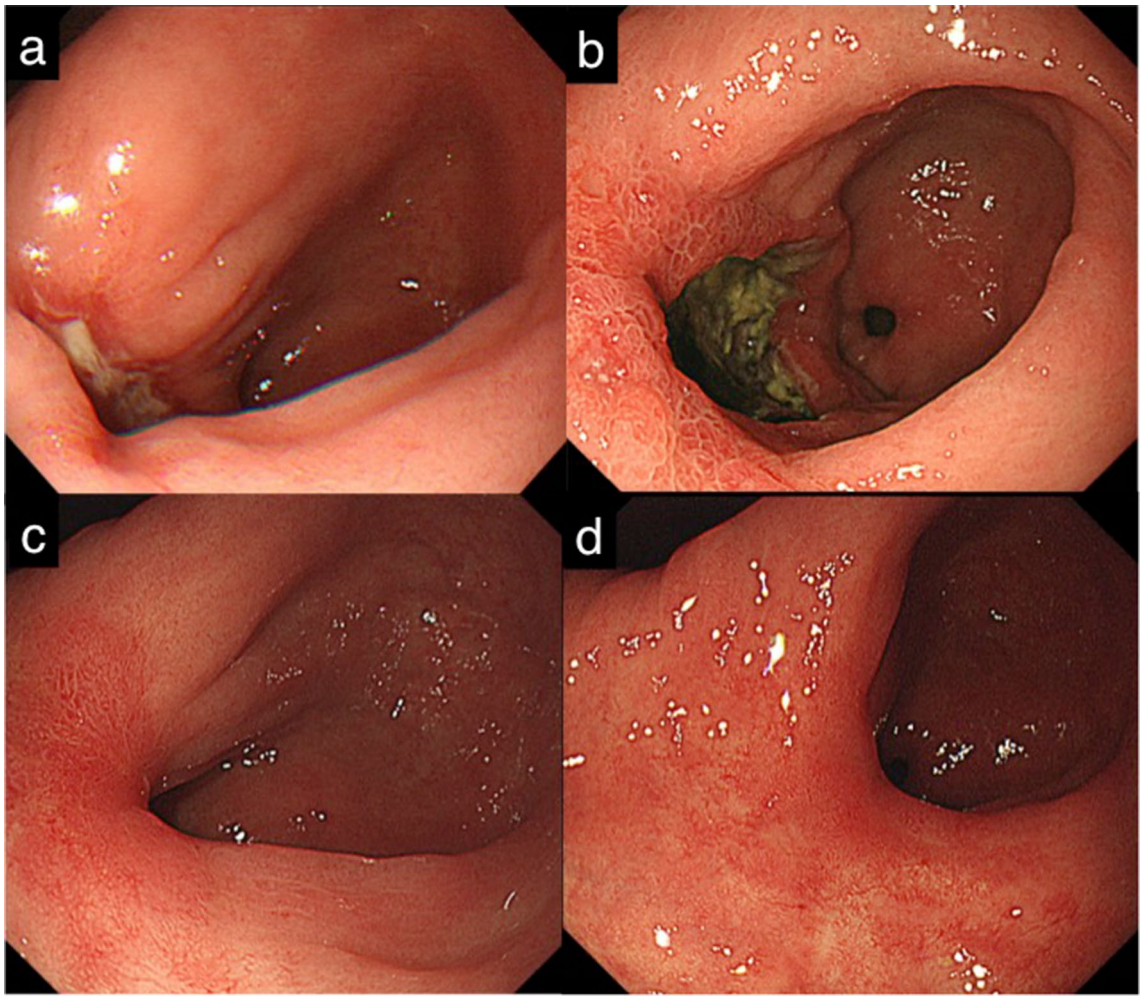


**Fig. 2** Images of esophagogastroduodenoscopy. **a** Shrinkage of primary lesion after two courses of S-1 plus oxaliplatin (SOX). **b** Regrowth of the tumor after five courses of SOX. **c** Scar lesion in the lower gastric corpus and biopsy specimen revealed no tumor cells after seven courses of nivolumab. **d** No recurrence of cancer 7 months from discontinuation of nivolumab

The primary lesion disappeared with EGD and CT showed the lymph nodes had shrunk and no peritoneum dissemination nodules (Fig. 2d). There were several small and low-density areas in the liver on the CT, without any uptake on PET-CT (Fig. 3d). As stable findings of these images continue, we assume that there are no viable cancer cells left, and we regard this status as clinical CR. Lower muscle weakness has been improved and he was followed without any sign of regrowth. He has survived 26 months from diagnosis and maintained clinical CR for 10 months after discontinuation of pharmacotherapy.

## Discussion

Cancer cells multiply by having various immune evasion systems, and one of them is the expression of programed death-1 ligand (PD-L1) which connects to programed death-1 (PD-1) on the T cell and blinds the immune reaction. Nivolumab is a humanized IgG4 and PD-1 monoclonal antibody that has demonstrated antitumor effect in various cancers, and has been administered to gastric cancer since 2017 in Japan.

We reported a rare case of successful treatment of metastatic gastric cancer with nivolumab in which the primary lesion disappeared, and clinical CR was assumed. In the ATTRACTION-2 trial, relatively high DCR up to 40.3% was reported [1], and the number of patients with CR increased from 0 to 3 (1.1%) during the 2-year follow-up [2]. In two other available reports CR was achieved [5, 6] (Table 1).

High expression of PD-L1 is associated with an increased response in various types of tumors including non-squamous cell lung cancer and squamous cell carcinoma of the head and neck (SCCHN), but irrelevant to gastric cancer [1]. The biomarkers of effective immunotherapies have explored, and microsatellite unstable tumors, positive for EBV, and

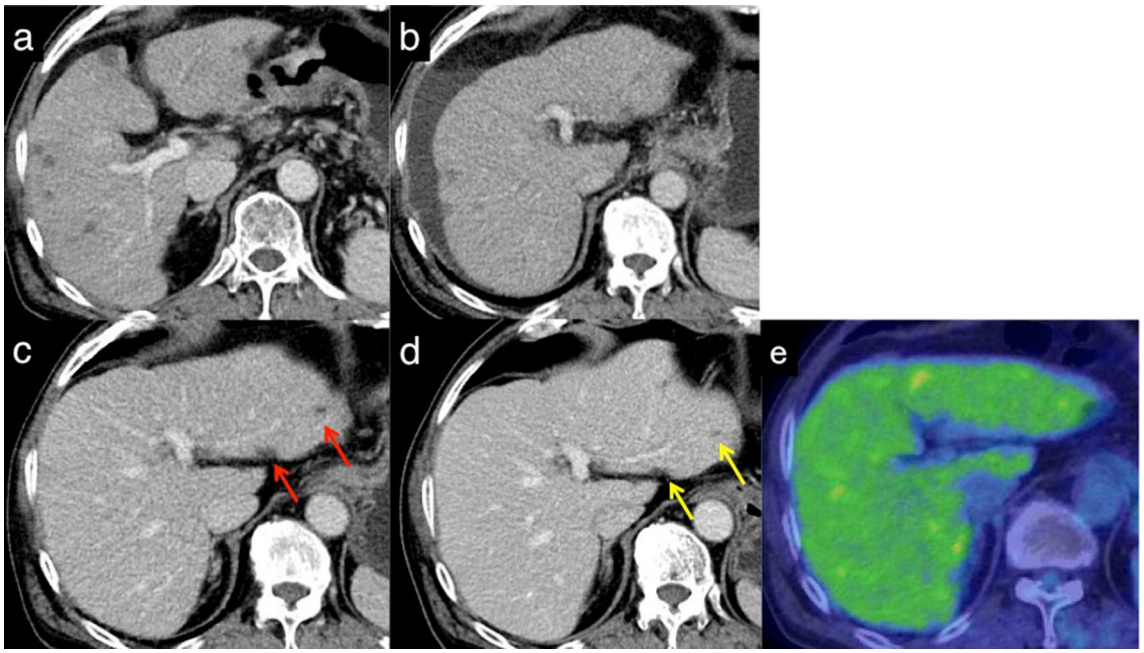


**Fig. 3** Images of computed tomography. **a** Significant shrinkage of liver metastases after two courses of S-1 plus oxaliplatin (SOX). **b** Recurrence of ascites on the liver surface, and further reduction of metastases after five courses of SOX. **c** Small low-density lesions in the liver after seven courses of nivolumab (red arrows) and **d** 7 months after discontinuation of nivolumab (yellow arrows). **e** No uptake on positron emission tomography CT

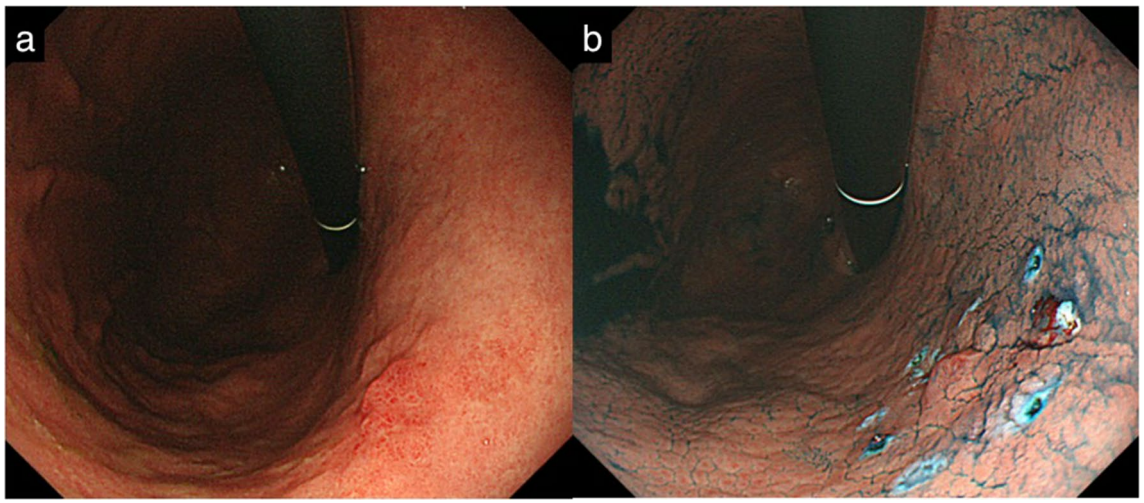


**Fig. 4** Images of esophagogastroduodenoscopy. **a** Another early gastric cancer was found on the lower gastric corpus, proximal side of the main lesion after five courses of S-1 plus xaliplatin. **b** The lesion remained stable even after 15 courses of nivolumab and endoscopic submucosal dissection was completed

tumor-infiltrating lymphocytes are the ones of possible prognostic factors [7–9]. Kim et al. reported dramatic responses to pembrolizumab in patients with metastatic gastric cancer; overall response rate 85.7% in MSI-H cancer and 100% in EBV-positive cancer [10]. However, none of the patients who achieved CR with nivolumab including our case had memorable backgrounds to expect tumor shrinkage (Table 1). In our case, metastatic gastric cancer showed a remarkable response to nivolumab, but another early gastric cancer remained stable. The efficacy of nivolumab may depend on the immunogenicity of synchronous cancers. But additional accurate investigations, including EBV status, were difficult because of not resecting primary tumor and its few residual biopsy specimen of the metastatic gastric

**Table 1** Characteristics of reported patients with CR

| No | Author | Sex | Age | Number of prior regimens | Residual tumor | MSI | PD-L1 | EBV |
|---|---|---|---|---|---|---|---|---|
| 1 | Chen [2] | M | 83 | 5 | Lymph node (#16, #104), liver, lung, abdominal cavity | Negative | Negative | – |
| 2 | | M | 63 | 3 | Lymph node (#16, #104, abdominal), lung | – | – | – |
| 3 | | M | 58 | 2 | Stomach, liver, pancreas, lymph node (#16, #104) | Negative | Negative | – |
| 4 | Namikawa [5] | M | 77 | 2 | Liver | – | – | – |
| 5 | Kashima [6] | M | 25 | 1 | Lymph node (#11p, #16b1, #104L, #108L) | Negative | Negative | Negative |
| 6 | Our case | M | 67 | 2 | Stomach, liver, lymph node (perigastric, #16), peritoneum dissemination | Negative | – | Undeterminable |

cancer. Further genetic or histochemical analyses are needed to find clinical responders to anti-PD-1 treatment.

We stopped administration of nivolumab after 15 courses because of irAE. There is some debate about when to stop treatment if a CR of the primary lesion is achieved without any adverse events. There is a report of patients whose target regions were distant lymph node metastases after total gastrectomy with para-aortic lymph node dissection that showed CR after finishing 21 courses of nivolumab [5]. No recurrence has been observed for 2 years after the discontinuation of therapy.

The 5-year follow-up of 129 patients with advanced non-small cell lung cancer (NSCLC) who received nivolumab for the maximum 2 years, showed 16 patients survived 5 years and 12 patients survived without progressive disease [3]. And in a study of 107 patients with advanced melanoma receiving nivolumab, 17 patients discontinued therapy for reasons other than disease progression, and 12 patients maintained responses after being off therapy for at least 16 weeks [4]. These prolonged effect was supported by a study reporting that nivolumab binds to T cell more than 20 weeks after the last infusion, regardless of the total number of nivolumab infusions or type of subsequent treatment [11]. These reports suggest that we can expect continuous antitumor effect of nivolumab as well as the likelihood of observing prolonged irAE after the therapy.

On the other hand, the favorability of continuing nivolumab was reported from CheckMate 153, a randomized study of nivolumab in patients with previously treated advanced NSCLC that compared continuous treatment vs treatment of a fixed 1-year period [12]. Though optimal treatment duration of nivolumab is under discussion after achieving CR, continuous therapy with nivolumab would be viable unless intolerable adverse events occur. Because of this case, we know that reluctant discontinuation of nivolumab does not always lead to disease progression.

Another important question concerns treatment strategy after the recurrence. There are some cases of achieving a second response to nivolumab [3, 13]. However, retreatment with nivolumab in patients who had required treatment interruption because of irAE led to 26% recurrence of initial irAE, and 26% of new irAE including two treatment-related deaths [13]. There are also some reports that describe efficacy of chemotherapy after progression with immunotherapy against NSCLC and SCCHN [14, 15]. We must make treatment decisions individually with much consideration of target lesions, possible intervention of surgery or radiation, adverse effect of pharmacotherapy, and patient's performance status.

We reported a case of metastatic advanced gastric cancer and another early gastric cancer that were successfully treated with combination of chemotherapy, immunotherapy, and ESD. Once a good reduction of cancer is achieved with nivolumab, though it is relatively rare, we can say that there is a possibility of prolonged effect that leads to better prognosis.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Informed consent** Informed consent was obtained from the patient in this report.

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