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Case Report

A Case of Advanced Gastric Cancer with Peritoneal Metastasis Treated Successfully with Nivolumab

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Keywords
Advanced gastric cancer · Peritoneal metastasis · Nivolumab

Abstract
Peritoneal metastasis (PM) is detected in 14% of gastric cancers at the time of initial diagnosis, with a median survival time of 4 months. A 66-year-old woman diagnosed with cT4a(SE) N2M1(LYN) cStage IV was treated with three lines of chemotherapy for a year. During the third line of chemotherapy, computed tomography (CT) scan revealed a large amount of ascites, periportal collar sign, and bilateral ureteral stenosis owing to PM. The tumor biomarkers (CEA and CA 19–9) remained elevated similar to the initial levels. The patient was administered 3 mg/kg nivolumab intravenously biweekly as the fourth line of chemotherapy. Three months after the nivolumab treatment, gastroscopy revealed an extreme reduction of the tumor size, while CT scan revealed the absence of ascites and a well-controlled tumor. There was no immune-related adverse event with nivolumab during and after the treatment, and performance status improved to 0. The patient has been alive for about 2.5 years since her first visit with her sixth line of chemotherapy (docetaxel). We report a case of advanced gastric cancer with PM that was treated successfully with nivolumab.

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Introduction

Advanced gastric cancer (AGC) has a poor prognosis, and palliative chemotherapy has been the only probable therapeutic option for patients with a median survival of 9–12 months. Peritoneal metastasis (PM) is detected in 14% of gastric cancers (GCs) at the time of initial diagnosis, with a median survival time of 4 months [1]. GC patients with PM cannot undergo radical surgery, and the chemotherapeutic effect is limited owing to blockage of intravenous chemotherapy drugs by the peritoneal barrier and tumor chemoresistance [2]. Nivolumab is a fully humanized monoclonal antibody that blocks the interaction of programmed cell death-1 (PD-1) with its ligand PD-L1 and has shown clinical efficacy in patients with various types of cancers [3–6]. In this study, we report about a GC patient with PM who was administered nivolumab as a fourth-line therapy and who showed long-term disease control.

Case Presentation

A 66-year-old woman presented with chronic epigastralgia for 2 months with significant weight loss. No medical or family history of any malignancy existed. Stomach gastroscopy revealed a thickened wall in the antrum area, which spread proximally to the cardia of the stomach and disturbed peristalsis (Fig. 1a). Endoscopic biopsy revealed an adenocarcinoma. Computed tomography (CT) scans showed gastric wall thickening and a high density of fat around the gastric wall, suggesting tumor infiltration into the gastric serosa and swelling of the para-aortic lymph nodes (Fig. 1b–d). We diagnosed this patient as having cT4a(SE)N2M1(LYN) cStage IV. S-1 and oxaliplatin (SOX) chemotherapy was administered. After three courses of SOX chemotherapy, the primary tumor markedly reduced in size, indicating a partial response. After another three courses of SOX chemotherapy, the para-aortic lymph nodes markedly increased in size, indicating a progressive disease. She was then treated with five cycles of ramucirumab and paclitaxel (RAM/PTX) as second-line chemo therapy and four cycles of CPT-11 as third-line chemotherapy. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) decreased to 2 during the course of a year of chemotherapy. CT scans showed a large amount of ascites, periportal collar sign, and bilateral ureteral stenosis owing to PM about 1 year after her first visit (Fig. 2a, b). The tumor markers remained elevated, similar to initial levels, indicating a transitive graph. The patient was administered 3 mg/kg nivolumab intravenously biweekly. The outcomes were judged after every 3 courses of nivolumab. Three months after the nivolumab treatment, gastroscopy revealed an extreme reduction in tumor size and wall thickness (Fig. 3a, b), whereas a CT scan revealed the disappearance of ascites and a well-controlled tumor (Fig. 3c, d). Immune-related adverse event with nivolumab did not appear during and after the treatment, and ECOG-PS improved to 0. However, 6 months after nivolumab administration, ureteral stenosis and swelling of the para-aortic lymph nodes occurred again. Nivolumab administration was replaced with SOX. Currently, the patient has survived under docetaxel treatment since approximately 2.5 years after her first visit.

Discussion/Conclusion

It has been clinically efficacious in patients with various types of cancers [3–6]. Immune-related adverse events of nivolumab monotherapy can affect many organs, including the lungs, colon, liver, endocrine glands, kidney, skin, and brain [7]. The ATTRACTION-2 study

found that administration of nivolumab to patients who were previously treated for advanced GC results in a significant survival benefit [8]. In a subgroup analysis of the ONO-4538–12 trial, there were no interactions between PM and nivolumab treatment, indicating that nivolumab is effective for treating GC patients with or without PM. Immune checkpoint inhibitors are expected to improve the outcome of GC patients with PM. Nivolumab has been used as third- and fourth-line chemotherapy in our institution since October 2017. In our institution, 23 patients were treated with nivolumab from October 2017 to March 2018. We observed one case that achieved partial clinical response out of 10 GC cases with PM, whereas three cases achieved partial response (PR) mediated by nivolumab among GC cases with liver metastasis and para-aortic lymph node metastasis. These cases did not have any blood toxicity, appetite loss, general fatigue, and bone marrow suppression, so as to receive the next regimen of chemotherapy. Mishima et al. showed that better PS was associated with longer overall survival following treatment with nivolumab [9]. Consistent with this result, nivolumab can contribute to anti-cancer effects and also improve patients' PS, so as to increase the chance of next chemotherapy.

We focused on prior treatment as first- and second-line therapy for stage IV GC. In the PR group of nivolumab (4 cases), complete response (CR) and PR percentages of prior treatment were higher than those in the stable disease (SD) and progressive disease (PD) groups. These results suggest that if a case achieves the anti-tumor effect by prior treatment, such as first- or second-line regimen, the effect will mostly likely be owing to nivolumab. Tumor-associated antigens released into the circulation are produced because of chemotherapy response. Furthermore, the released circulating tumor antigens provides an identifiable target surface on the tumor cell that might be used for in vivo diagnosis or antigen-directed therapy. We assume it is the reason why nivolumab sensitivity to the tumor was elevated. These representations are shown in several other reports. Kobayashi et al. reported that responders to chemotherapy or curative-intent chemoradiotherapy immediately before nivolumab monotherapy had better responses to nivolumab monotherapy than non-responders to previous chemotherapy or curative-intent chemoradiotherapy [10]. Immunogenic tumor cell death caused by chemotherapy can stimulate anticancer immune effectors [11]. The abscopal effect refers to tumor regression at a site distant from the primary tumor because of radiotherapy [12] and is thought to depend on the activation of the immune system [13–14]. In addition, Nakano et al. found that cells positive for the exhaustion markers PD-1 and T-cell immunoglobulin and mucin domain 3 (TIM-3) and cells co-expressing PD-1 and TIM-3 abundantly exist among malignant ascites and tumor-infiltrating lymphocytes [15]. We believe that the sensitivity of nivolumab to the tumor, even in the ascites, was elevated. Tumoral and lymphocyte-derived immunohistochemical staining for PD-1, PD-L1, and tumor mutational burden have has shown potential as predictive response biomarkers in several tumor types. Optimal incorporation of immune-mediated therapies into GC is an area that is being investigated intensely, and its benefits have been demonstrated in smaller studies of advanced patients. Important questions of biomarker selection, roles of molecular characterization, optimal combinatorial approaches, and therapeutic sequencing remain [16]. Biomarker analysis is under investigation. Results from multiple ongoing trials in GC will further refine the roles of biomarker selection and optimal combination approaches. This is the first report of AGC with PM that was successfully treated with nivolumab.

Acknowledgement

We would like to thank the patient for giving us her consent to publish the results.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Disclosure Statement

The authors have no conflicts of interests to declare.

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Author Contributions

HT, TS, and TK wrote the manuscript. TS diagnosed this case. HT and TS performed the chemotherapy. All authors conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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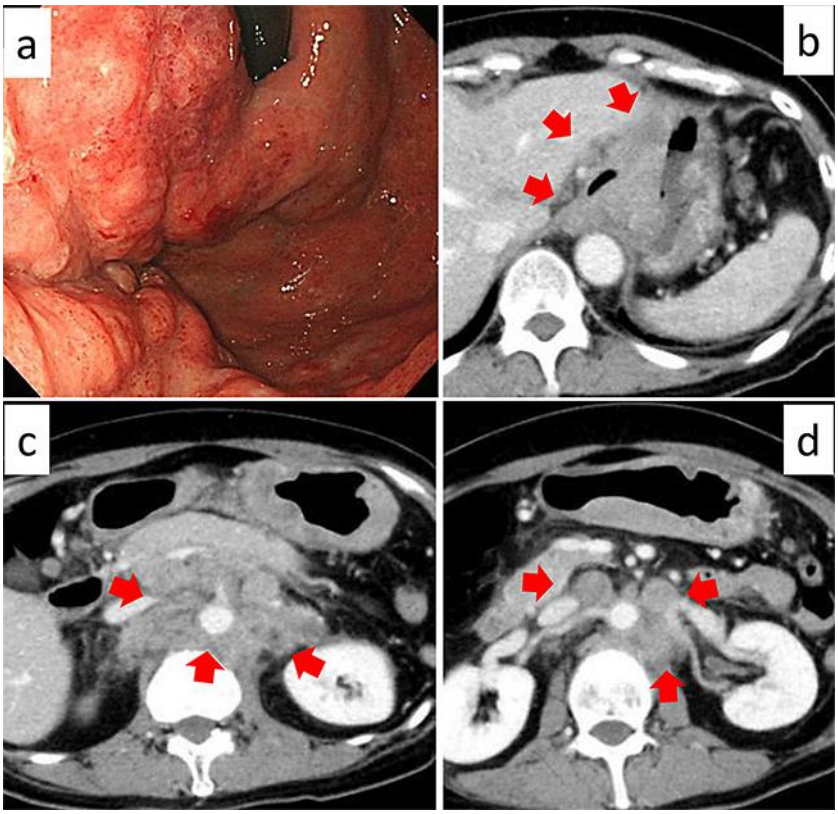

Fig. 1. **a** Gastroscopy showed thickened wall in the antrum area, and spread proximally to the cardia. **b**, **c** CT showed high density of fat around the gastric and swelling of para-aortic lymph nodes, and bilateral adrenal metastasis (red arrows).

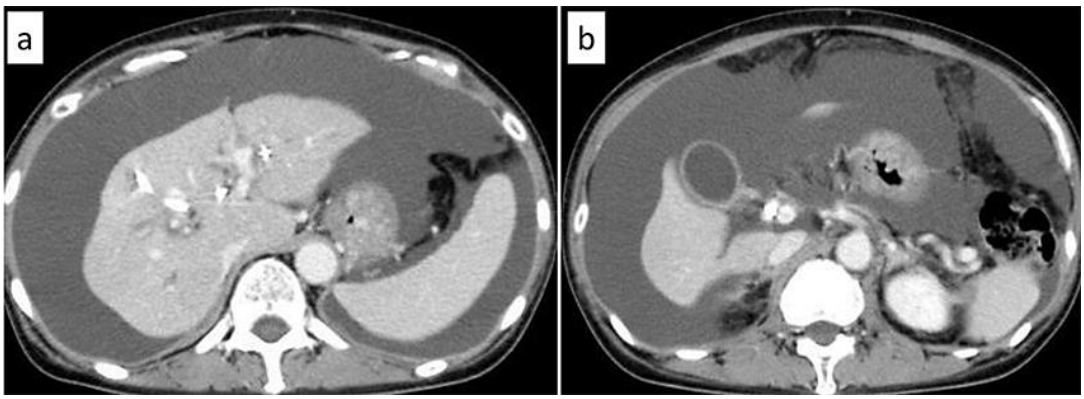

Fig. 2. **a**, **b** CT showed large amount of ascites, periportal collar sign, and right ureteral stenosis due to peritoneal dissemination.

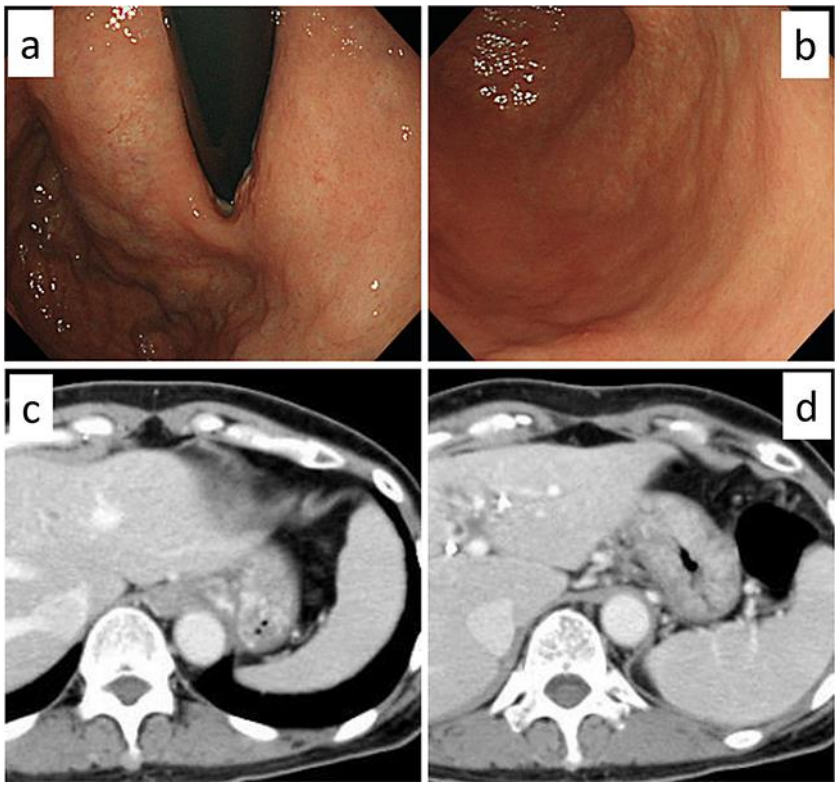

Fig. 3. **a**, **b** Gastroscopy showed reduction tumor extremely and thin-walled. **c**, **d** CT showed ascites disappearance and well-controlled tumor.