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Confirmed Pathological Response to Nivolumab Combined with Chemotherapy for Advanced Gastric Cancer with Left Subclavicular Lymph Node Metastasis: A Case Report

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We report the case of a 44-year-old male with advanced gastric cancer with distal lymph node metastasis who achieved a pathological complete response to chemotherapy combined with nivolumab. After five months of treatment, the patient underwent total gastrectomy with D2 lymph node dissection, and histological examination revealed the absence of malignant cells not only in the resected specimen but also in the harvested lymph nodes. At present, more than 1 year after the initial surgery, the patient is still alive without any recurrence. This case highlights the potential of chemotherapy combined with nivolumab to induce a complete response in advanced gastric cancer patients.

Keywords: advanced gastric cancer; conversion chemotherapy; curative resection; nivolumab; pathological complete response
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Introduction

Gastric cancer is a common and deadly malignancy with a poor prognosis, especially in advanced stages (Sung et al. 2021). The development of immune checkpoint inhibitors (ICIs) has improved the treatment options for advanced gastric cancer, with nivolumab showing promising results (Shen and Wang 2022). However, the optimal use of nivolumab in combination with chemotherapy and the potential for achieving a complete response remain uncertain. Here, we report the case of a patient with advanced gastric cancer who achieved a complete response (CR) to chemotherapy combined with nivolumab.

Case Presentation

A 44-year-old man with upper abdominal pain and anemia was referred to our hospital with advanced gastric cancer detected at a clinic by gastrointestinal endoscopy.

A preoperative abdominal computed tomography (CT) scan revealed wall thickening with dark staining mainly in the gastric body, suggesting gastric cancer. Perigastric, hepatic hilar, and splenic and left supraclavicular lymph node swelling suggested multiple lymph node metastases (Fig. 1a, b). The serum carcinoembryonic antigen (CEA) level was 86.1 ng/ml, and the carbohydrate antigen (CA) 19–9 level was less than 2.00 U/ml. Gastrointestinal endoscopy revealed a Borrmann type 4 tumor from the cardia to the gastric body (Fig. 2a, b). Biopsy of the specimen revealed that the tumor was a poorly differentiated adenocarcinoma (Fig. 2c). Immunohistochemically, the tumor was negative for human epidermal growth factor receptor 2 (HER2) protein expression. The programmed death-ligand 1 (PD-L1) combined positive score (CPS) was 5 or greater (Fig. 2d). Multiplex PCR fragment analysis of tumor cells

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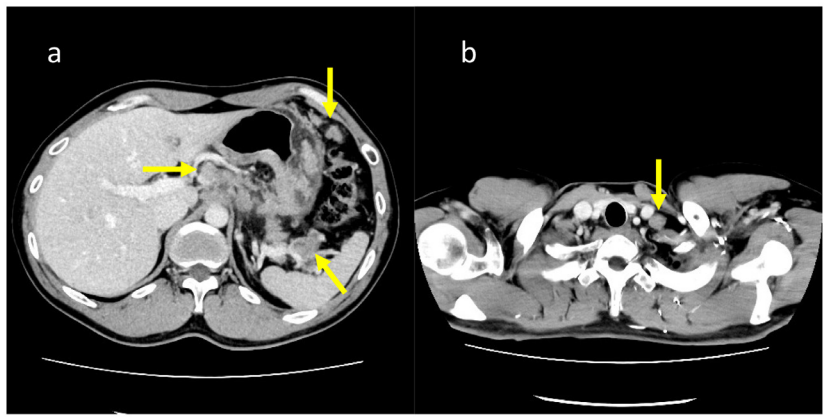

Fig. 1. Abdominal computed tomography (CT) scan before chemotherapy.
(a) Wall thickening with dark staining mainly in the gastric body, suggesting gastric cancer; perigastric, hilar, and splenic lymphadenopathy suggestive of multiple lymph node metastases; (b) Left supraclavicular lymph node swelling.

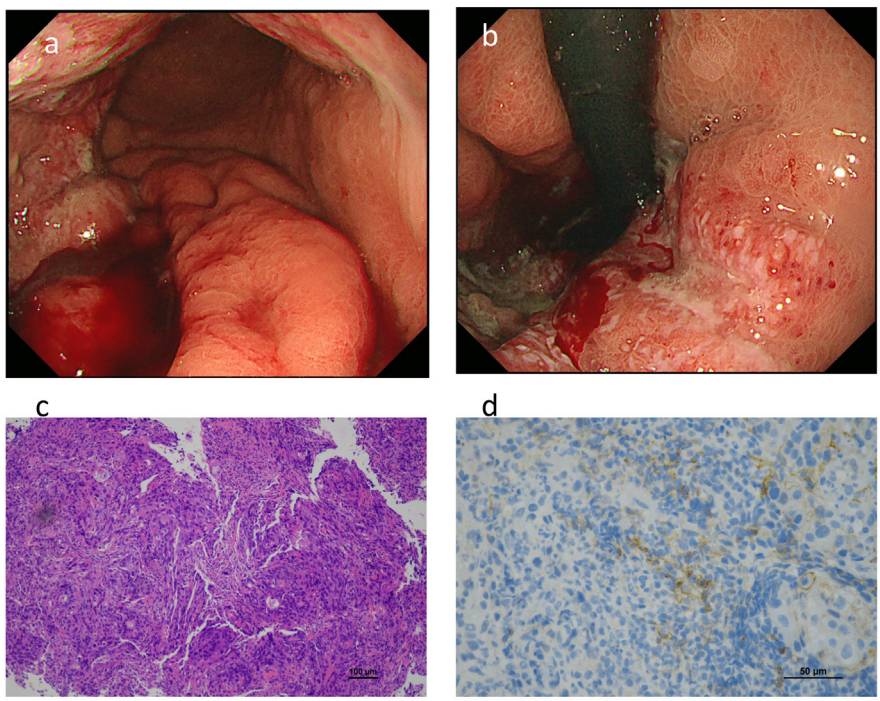

Fig. 2. Gastrointestinal endoscopy findings and pathology.
(a, b) Borrmann type 4 tumor from the cardia to the gastric body at initial diagnosis; (c) biopsy of the specimen revealing that the tumor was a poorly differentiated adenocarcinoma; (d) PD-L1 combined positive score (CPS) of 5 or more.

revealed microsatellite stability (MSS).

The initial stage was cT4N3M1, stage IV, according to the 8th Union for International Cancer Control (UICC) TNM classification (Brierley et al. 2017). Initially, we recommended prolonging his life with systemic chemotherapy. We recommended a regimen that included fluorinated pyrimidine, oxaliplatin and nivolumab (NIVO). Since he was a billiard player and had a large tournament coming up, he wanted treatment for less CIPN until then. The patient received two cycles of S-1 plus cisplatin as a less-CIPN-risk regimen compared with oxaliplatin, followed by five cycles of S-1, carboplatin and nivolumab. After 5 months of chemotherapy, CT showed gastric tumor shrinkage, but node swelling was not identified (Fig. 3a). Additionally, positron emission tomography-CT (PET-CT) showed no significant accumulation of either primary gastric tumor or lymph node metastases (Fig. 3b). Gastrointestinal endoscopy also showed that the gastric tumor had shrunk and scarred (Fig. 3c, d).

Since chemotherapy was remarkably effective, we considered that a radical cure could be achieved by surgical resection. The patient then agreed to undergo surgery. First, staging laparoscopy showed no obvious peritoneal dissemination, and total gastrectomy with D2 lymph node

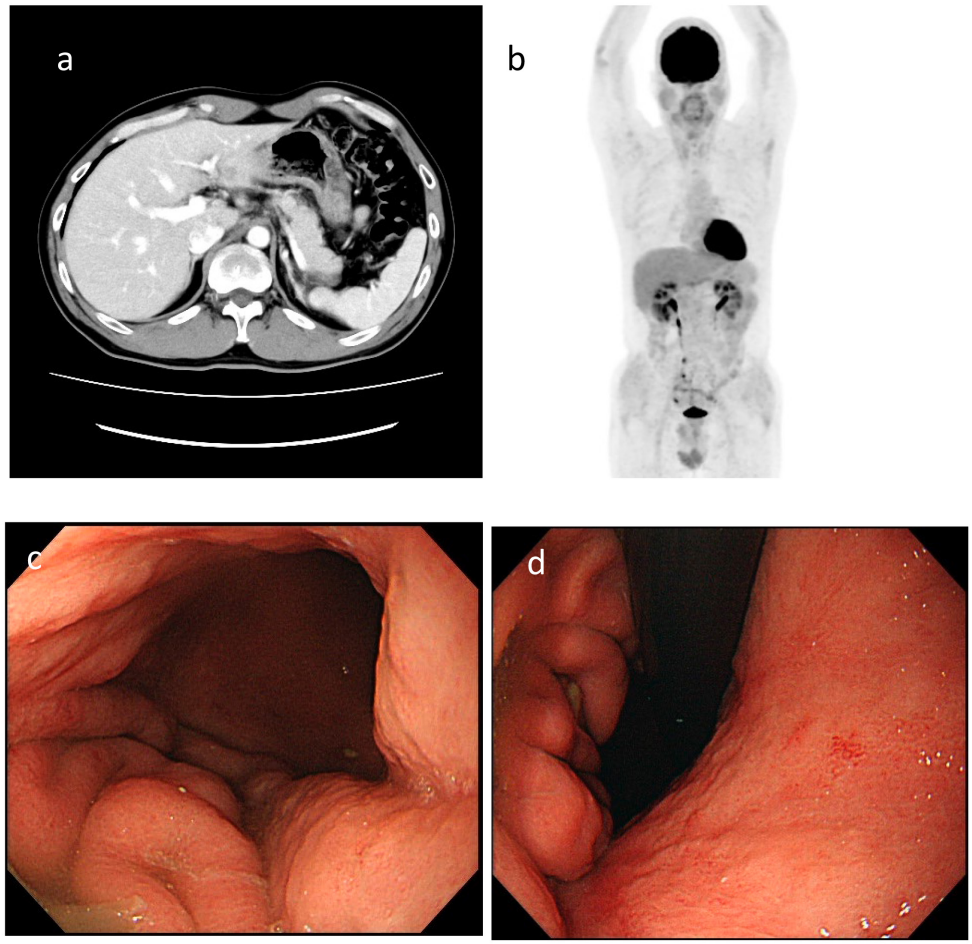

Fig. 3. Perioperative images.
(a) Computed tomography (CT); (b) positron emission tomography revealing no nodules; (c, d) gastrointestinal endoscopy showing that the gastric tumor had shrunk and scarred.

dissection was performed. The patient's postoperative course was uneventful. He was discharged on the fourteenth postoperative day. Pathology of the resected tissue revealed no tumor cells in either the stomach or abdominal lymph nodes (Fig. 4a-c). The final pathological diagnosis was type 4, negative for viable cancer cells, Ly 0, V 0, ypPM 0, ypDM 0, ypN 0 (0/34), cM0, ypStage 0 according to the TNM classification (8th edition), and tumor regression grade 3. Although pathological complete response (pCR) was achieved for the primary gastric cancer, there was a possibility of minimal residual tumor in the subclavian lymph node, and chemotherapy including nivolumab was continued after surgery. However, chemotherapy was interrupted after 2 months due to immune-related adverse events (type 1 diabetes mellitus and interstitial lung injury). After stopping chemotherapy, the patient has remained treatment-free for more than 1 year (more than 1 year and 6 months after surgery) with no apparent recurrence.

Discussion

Gastric cancer, particularly in advanced stages, continues to represent a substantial clinical challenge due to its typically poor prognosis (Wagner et al. 2006). The advent of ICIs, such as nivolumab, has led to the introduction of new treatment modalities, improving survival rates in some patients (Wagner et al. 2006, Shen and Wang 2022). However, achieving a pCR, as observed in this case, remains an exceptional outcome. The achievement of pCR implies that there are no detectable cancer cells in the resected tissue or lymph nodes postoperatively, suggesting a highly effective response to neoadjuvant treatment (Cho et al. 2015). Endo et al. (2020) reported a case of early gastric cancer coexisting with advanced lung cancer in which nivolumab administered for lung cancer resulted in shrinkage of the gastric cancer, and pCR was confirmed by surgery. To our knowledge, this is the first report of CR confirmed by surgery after nivolumab-containing chemotherapy for advanced gastric cancer. This report provides valuable clinical evidence supporting the possible benefits of combining nivolumab with chemotherapy in the treatment of advanced gastric cancer.

Recently, several clinical trials have shown the efficacy of immune checkpoint inhibitors in advanced gastric cancer. In the ATTRACTION-2 trial, nivolumab, a pro-

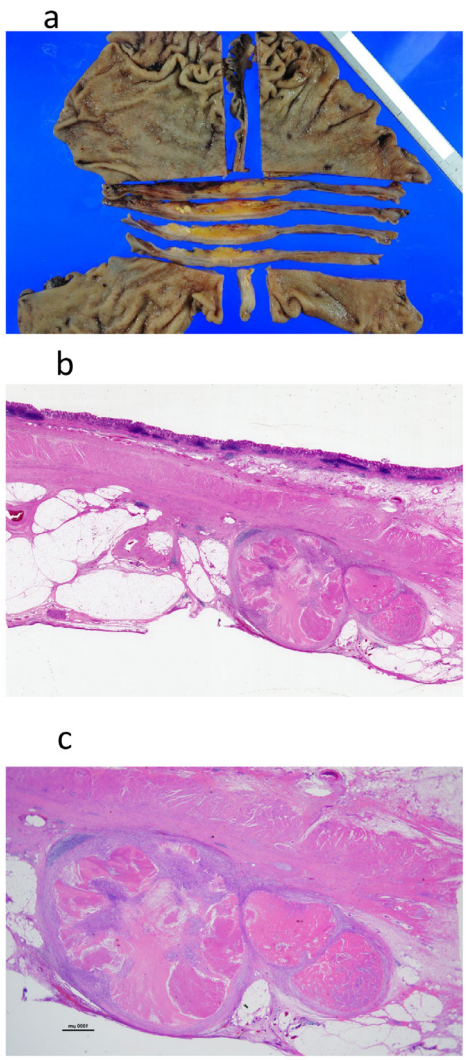

Fig. 4. Gross pathology images of surgical specimens.
(a) External surface of the resected stomach; histological findings by hematoxylin and eosin staining; (b) malignant cells that disappeared from the resected stomach; (c) fibrotic tissue that was found to have replaced the cancer in the dissected lymph node.

grammed death 1 inhibitor, improved overall survival (OS) compared to placebo in patients who had previously received at least two chemotherapy regimens (Kang et al. 2017). Additionally, the CheckMate-649 trial demonstrated that nivolumab plus chemotherapy improved OS and progression-free survival (PFS) compared to chemotherapy alone as a first-line therapy in patients with advanced gastric cancer or gastroesophageal junction cancer (Janjigian et al. 2021). The KEYNOTE-062 trial, which investigated pembrolizumab plus chemotherapy as a first-line therapy, also revealed a survival benefit in a population with high PD-L1 expression (Shitara et al. 2018). The complete response (CR) rates in these trials ranged from 3.5-19.3%, but in advanced gastric cancer, clinical CR determinations were based solely on imaging and endoscopy. In this case, gastrectomy was performed, and a pathologic CR was proven, which led to a more accurate determination. For patients with a PD-L1 CPS > 5 or MSI-high status who are expected to respond to ICI therapy, treatment aimed at conversion surgery may be possible even for advanced cancer with distant metastasis.

The role of surgery after a substantial tumor response is achieved remains a topic of debate. For patients with microsatellite instability–high (MSI-H) metastatic gastric cancer, 6-8% of which are advanced cancer patients (Pietrantonio et al. 2019), a favorable response can be expected with the administration of ICIs (Kim et al. 2018). Clinical trials are ongoing to investigate the strategy of omitting surgery in MSI-H gastric cancer patients who have responded well to ICIs preoperatively, but these data are still immature (Raimondi et al. 2021, Andre et al. 2022). Currently, there are limited data from which we are able to validate the omission of surgery completely for these patients.

This case illustrates the potential of nivolumab combined with chemotherapy for inducing a complete response in advanced gastric cancer patients. However, importantly, additional studies are needed to determine the optimal use and sequence of these therapies, their long-term effects, and the factors predicting the response to these treatment strategies.

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Author Contributions

N.M. designed the study; N.I. and F.K.N. contributed to the preparation of pathological tissue specimens; N.M. drafted the original manuscript; Y.S. and K.M. supervised the conduct of this study; and all the authors reviewed the manuscript draft and revised it critically on intellectual content. All the authors approved the final version of the manuscript to be published.

Conflict of Interest

The authors declare no conflict of interest.

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