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CASE REPORT

A case of gastric cancer with delayed onset of tumor reduction effect by nivolumab therapy

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Abstract
Immune checkpoint inhibitors may have different clinical effects compared with conventional anticancer drugs. An 85-year-old male received chemotherapy for recurrent gastric cancer. As liver metastasis progressed, nivolumab was introduced as a fourth line treatment. Progression of liver metastasis in size was observed in CT after 3 courses of nivolumab therapy. Nivolumab treatment was discontinued, because the general condition of the patient also worsened. However, his general condition improved as hepatobiliary enzyme levels, inflammatory response, and tumor markers improved. Liver metastasis was shrinking on the image, so we resumed nivolumab therapy. To the authors' knowledge, this is the first case of pseudoprogression undergoing immunotherapy for gastric cancer. In this case, the antitumor effect was exhibited in a delayed manner and the tumor shrinkage was obtained.

Keywords Gastric cancer · Nivolumab · Pseudoprogression · MSI

Introduction

Programmed cell death (PD)-1 immune checkpoint inhibitors have been used to treat various types of tumors. Taking the results of the ATTRACTION-2 study, nivolumab was approved for the treatment of advanced and recurrent gastric cancer in Japan [1]. Compared with conventional cytotoxic agents, therapeutic effects of immune checkpoint inhibitors are different; pseudoprogression is reported as one of the unique phenomena with immune therapeutic agents [2, 3]. In pseudoprogression, radiologic enlargement of the tumor followed by tumor reduction is typical findings. To the best of our knowledge, there is no report on pseudoprogression in gastric cancer yet, and details have not been clarified. Here, we report a recurrent gastric cancer case which showed delayed shrinkage of liver metastasis after cessation of nivolumab treatment.

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Case report

An 85-year-old male received total gastrectomy for gastric cancer. Histological diagnosis was well-differentiated adenocarcinoma, T3(SS), N2, M0, pStageIIIA, according to Japanese Classification of Gastric Carcinoma, the 14th Edition. He received postoperative adjuvant chemotherapy with S-1 (100 mg on day 1–28, every 42 day) for 1 year. 4 years and 2 months after surgery, a solitary metastasis in the posterior lobe of the liver appeared. Considering his age of over 80 years, we started treatment with S-1 monotherapy, followed without new lesions, and chemotherapy was changed in order of paclitaxel + ramucirumab, irinotecan along with exacerbation of liver metastasis and treatment was continued. Because tumor enlarged to 14 cm and judged to be resistant to conventional cytotoxic agents (Fig. 1a), nivolumab was introduced (3 mg/kg, every 2 week) as the fourth line treatment. After receiving three cycles of nivolumab (6 weeks later), CT demonstrated enlargement of liver metastasis which was assessed as progressive disease (growth rate of 21%) in Response Evaluation Criteria in Solid Tumors (RECICT) 1.1 and it was judged that there is no treatment effect (Fig. 1b). Moreover, general fatigue worsened as his performance status became 2 (PS 2). We decided to stop nivolumab therapy and adopted a policy

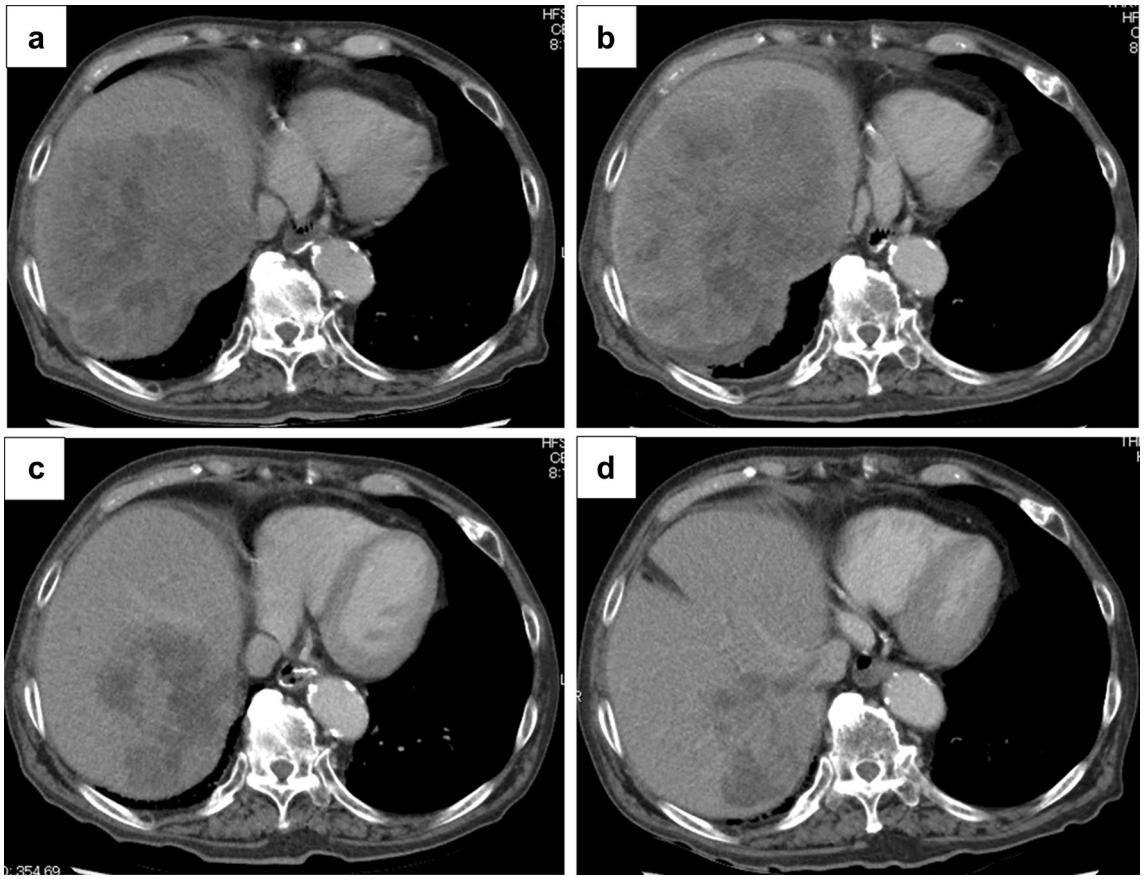

Fig. 1 **a** CT before introduction of nivolumab. A liver metastasis of 14 cm occupying the right lobe of the liver. **b** CT after 3 courses of nivolumab therapy. Liver metastasis was enlarged to **a** maximum diameter of 17 cm. **c** CT after 5 courses of nivolumab therapy. **d** CT after 8 courses of nivolumab therapy. Liver metastasis tends to shrink over time

of palliative care. The tumor markers and hepatobiliary enzymes decreased over time (Fig. 2), subjective symptoms such as malaise gradually improved. Ultrasonography of the abdomen revealed that liver metastasis reduced to 10 cm in diameter and the tumor shrinkage effect was delayed. We restarted nivolumab therapy, and tumor was on a contraction tendency also on CT (Fig. 1c, d). Following a remarkable response to immunotherapy, the specimen at the time of gastrectomy was examined by immunohistochemical staining to investigate mismatch-repair deficiency of the tumor. In our case, protein expression of PMS2, one of mismatch-repair genes, was not observed (Fig. 3). The patient is still ongoing nivolumab treatment without severe side effects.

Discussion

The ATTRACTION-2 study found that nivolumab administered to patients with advanced gastric cancer produces a significant survival benefit, but an objective response rate was 11.2% [1]. Immune checkpoint inhibitors sometimes show different therapeutic effects compared with conventional cytotoxic chemotherapeutic agents. Nivolumab occasionally induces pseudoprogression in various types of cancers [4–6]. Though the mechanisms of pseudoprogression are not yet fully disclosed, either continued tumor growth until a sufficient immune response occurs, or an infiltration of immune cells to the tumor burden is reported as a cause [2, 7]. The case which shows pseudoprogression associated with nivolumab therapy is rare in various types of cancers [2, 4, 5]. There have been no reports of pseudoprogression of gastric cancer. Our case was thought to be pseudoprogression in that it showed late tumor shrinkage effect, and it is particularly interesting that therapeutic effect persisted to produce considerable tumor shrinkage after cessation of nivolumab treatment. Details on the continuation of the tumor shrinkage effect even after the discontinuation of treatment are unknown, but it is possible that the therapeutic effect was continued by memory of immunity.

In recent years, it has been clarified that the therapeutic effect of the immune checkpoint inhibitor is related to microsatellite instability (MSI) or mismatch-repair

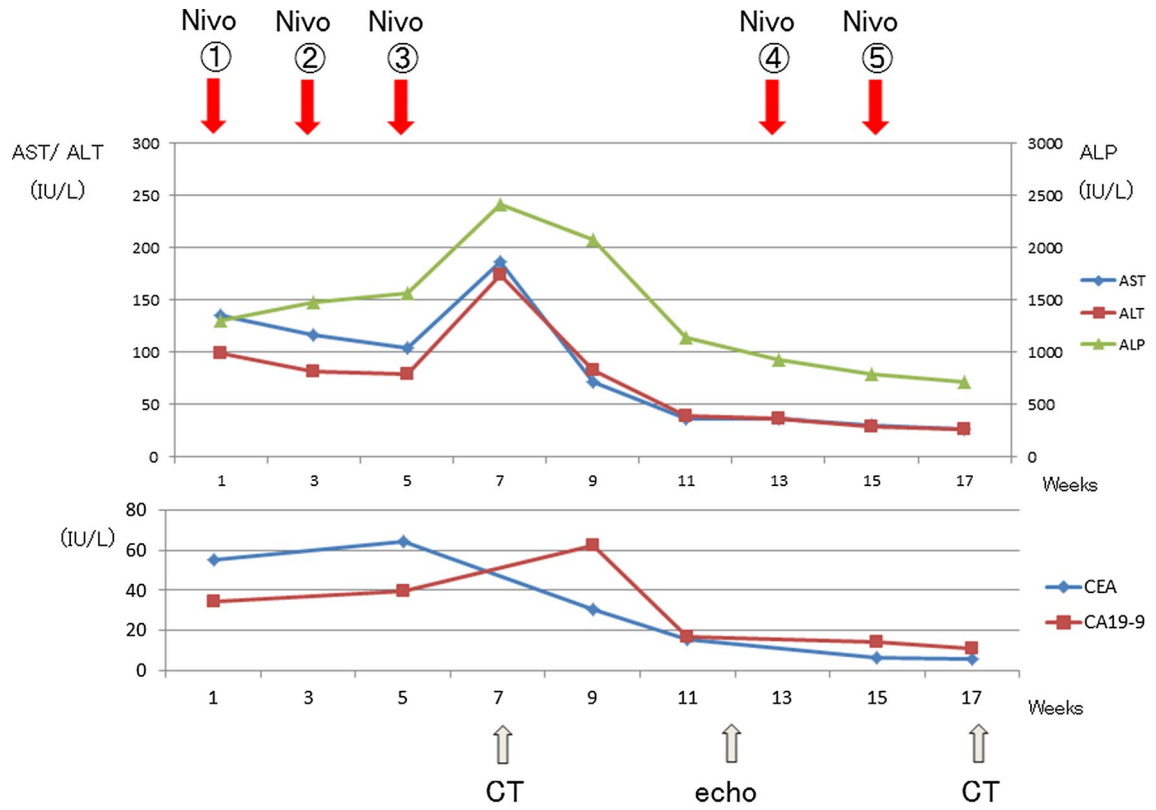

Fig. 2 Clinical course and blood test findings. Temporary hepatobiliary system enzymes and tumor markers showed elevated and then declined over time

deficiency (dMMR) of the tumor [8, 9]. MSI-high (MSI-H) tumors have common histopathological features such as lymphocytic infiltration, numerous somatic mutations, and expression of neoantigens [8]. Since these neoantigens are targets of the immune system, tumors may be susceptible to immunotherapy. In addition, the lymphocytes infiltrating into MSI-H tumors have enhanced expression of immune checkpoints like PD-1 and PD-L1. The proportion of MSI-H tumors in gastric cancer is reported as 5–22% [10, 11]. Our case was very well treated with nivolumab, tumor shrinkage was obtained, and the property of MSI-H might have contributed to success in response. Although the frequency of MSI-H is rare, it was suggested that MSI test may be useful for predicting the effect of treatment also in gastric cancer cases.

In conclusion, in this case, the general condition worsened with the enlargement of the tumor, but it was thought that tumor shrinkage was obtained after the treatment effect was delayed afterwards. Even in the case of nivolumab therapy for gastric cancer, it was suggested that it was necessary to observe the disease continuously after being judged as progressive disease and stopping medication.

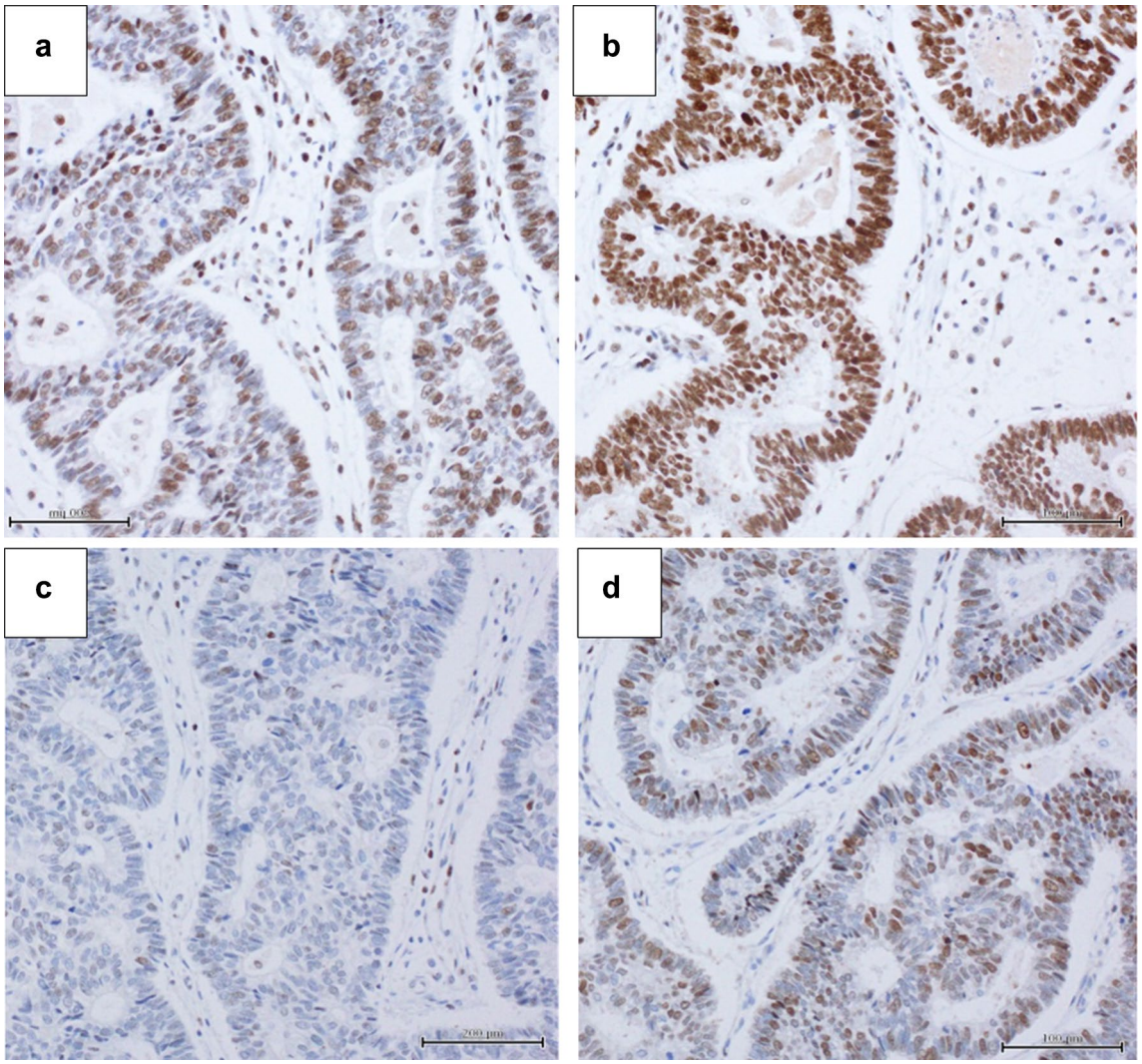

Fig. 3 Immunohistochemistry for mismatch-repair proteins of gastric cancer surgical specimen. **a** MLH1, **b** MSH2, **c** PMS2, **d** MSH6. (×200). PMS2 expression has disappeared

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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