Successful treatment with nivolumab in a patient with gastric cancer with severe liver failure resulting from multiple liver metastases: A case report

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Abstract. Gastric cancer (GC) is a globally prevalent and deadly malignancy often diagnosed at advanced stages, which can be accompanied by liver metastases. Conventional chemotherapy is contraindicated in patients with severe liver failure because several chemotherapeutic agents are metabolized by the liver. The present study reports on the successful use of nivolumab in a patient with advanced GC and severe liver failure owing to multiple liver metastases. A 57-year-old man was admitted to Shimane Prefectural Central Hospital (Izumo, Japan) with a 2-week history of appetite loss and jaundice. An upper gastrointestinal endoscopy revealed advanced GC (type IV). Computed tomography examination confirmed wall thickening of the gastric pylorus and the presence of multiple liver metastases. A gastric mucosal biopsy confirmed the diagnosis of HER2-positive gastric adenocarcinoma. S-1 + cisplatin chemotherapy was initiated but had to be halted due to the rapid deterioration in liver function, ultimately leading to acute liver failure. The patient was discharged from the hospital under palliative care. The patient was referred to Shimane University Hospital (Izumo, Japan) for a second consultation. Upon admission, the patient presented with severe liver failure, a Child-Pugh score of 10 (Class C), elevated total bilirubin levels of 13.9 mg/dl (normal range: <1.8 mg/dl) and elevated CEA and CA19-9. Nivolumab treatment was initiated, and notably, there was a substantial reduction in bilirubin levels, an improvement in liver function after a single cycle and a partial response observed in imaging studies. Despite the initial poor prognosis, the patient achieved long-term survival, ultimately succumbing to the illness 2 years and 6 months following the initiation of treatment. The present case underscores the potential of immune checkpoint inhibitors, such as nivolumab, in the treatment of patients with cancer and severe liver failure. It also challenges the conventional constraints of chemotherapy, offering a promising direction for future research in this area.

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Abbreviations: GC, gastric cancer; CT, computed tomography; ICIs, immune checkpoint inhibitors; LDH, lactate dehydrogenase

Key words: severe liver failure, multiple liver metastases, immune checkpoint inhibitors, GC, nivolumab

Introduction

As of 2020, gastric cancer (GC) is among the most prevalent malignancies globally, accounting for approximately one million newly diagnosed cases and an estimated 770,000 cancer-related deaths annually (1). This staggering prevalence makes GC the third leading cause of cancer-related mortality worldwide. Unfortunately, GC diagnosis often occurs at advanced or metastatic stages, making the tumor unresectable through surgery (2). Among these cases, distant metastases markedly diminish overall patient survival. The most common metastatic site is the liver, accounting for 17.4% of all metastatic occurrences (3).

The primary treatment option for patients with advanced GC is systemic chemotherapy. The conventional treatment regimens typically include fluorinated pyrimidines and platinum-based agents (4,5). However, patients with liver failure cannot tolerate cytotoxic agents because they are primarily metabolized by the liver. Consequently, case reports in the literature detailing chemotherapy administration in patients with severe liver failure are limited.

Recently, immune checkpoint inhibitors (ICIs) have gained prominence for treating various cancers, including GC. ICIs relieve the inhibition of T cell activation by binding to immune checkpoint molecules such as programmed cell death protein 1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thus triggering strong antitumor effects. Importantly, their use is not contraindicated, even in the presence of severe liver failure (6). Nevertheless, documented cases of treating patients with cancer and severe liver failure using ICIs are limited. Only two instances have been reported: One in 2017 involving the use

of nivolumab for a patient with Hodgkin lymphoma (7), and another in 2021 where pembrolizumab was administered to a patient with non-small cell lung cancer (8). Therefore, their application in advanced GC with severe liver failure remains relatively uncharted territory.

We herein report a case in which, for the first time in GC cases, long-term survival was achieved using ICIs in a patient with cancer and concomitant severe liver failure.

Case report

A 57-year-old man presented to Shimane Prefectural Central Hospital (Izumo, Japan) with a 2-week history of appetite loss and jaundice in April 2020 to be admitted on the same day. An upper gastrointestinal endoscopy revealed advanced gastric cancer (type IV). Computed tomography (CT) examination confirmed wall thickening of the gastric pylorus and multiple liver metastases (Fig. 1). A gastric mucosal biopsy confirmed the diagnosis of HER2-positive gastric adenocarcinoma (Fig. 2). Chemotherapy with S-1 + cisplatin was initiated promptly; however, hepatic impairment worsened during the first course. The patient was deemed unsuitable for continuing chemotherapy owing to rapidly elevated bilirubin levels, acute liver failure, and deteriorating performance status. He was discharged for palliative care.

After seeking a second opinion, he was referred to Shimane University Hospital (Izumo, Japan) the following month. On admission, the patient presented a performance status (ECOG) score of 3. Laboratory results indicated severe liver failure with a total bilirubin level of 13.9 mg/dl (normal range: <1.8 mg/dl) and a lactate dehydrogenase (LDH) level of 2,182 U/l (normal range: 135-214 U/l), alongside elevated tumor markers (CA19-9: 992 U/ml, CEA: 2,700 ng/ml) (Fig. 3). CT images indicated no cholestasis. The patient's Child-Pugh score was 10 (Class C). Based on these findings, the patient was diagnosed with HER2-positive unresectable gastric cancer (cStage IV, TNM) and severe liver failure.

Following admission, we promptly commenced nivolumab treatment (240 mg every 2 weeks) upon obtaining informed consent from the patient. After one cycle of chemotherapy, the total bilirubin level decreased from 13.9 to 3.6 mg/dl, and LDH decreased from 2,182 to 268 U/l. Furthermore, hepatomegaly and performance status improved, resulting in a partial response as observed in CT images (Fig. 4). The side effects were mild, characterized by a grade 1 immune-related skin rash (CTCAE, ver. 5.0). The typical side effects associated with conventional chemotherapy, such as nausea, vomiting, and bone marrow suppression, were completely absent. Instead, the patient's quality of life improved noticeably, marked by increased food intake and improved activity levels. After four treatment cycles, he presented with progressive disease; however, his performance status and liver function had improved notably. We switched to a chemotherapy regimen involving trastuzumab, oxaliplatin, and capecitabine [referred to as Cape-OX-T treatment; trastuzumab 6 mg/kg (initially 8 mg/kg) on day 1 every 3 weeks, oxaliplatin 130 mg/m^2 on day 1 every 3 weeks, capecitabine 2,000 mg/m^2 on days 1-14 every 3 weeks]. Oxaliplatin was omitted for the initial six cycles owing to renal and liver impairment. This combination therapy achieved normal levels of total bilirubin, LDH, and tumor markers, leading to size reduction of the metastatic liver tumor (Figs. 3 and 5). The patient died 2 years and 6 months after the treatment initiation, representing a notable long-term survival.

Discussion

The introduction of ICIs has unequivocally reshaped the therapeutic landscape of solid tumors. Notably, in the ATTRACTION-2 trial, aimed at investigating the efficacy of nivolumab in patients with recurrent and refractory GC, ICIs demonstrated a markedly prolonged overall survival compared to placebo (9). Nevertheless, prior crucial clinical trials have consistently excluded patients with severe organ dysfunction, particularly advanced liver failure. Regarding the application of chemotherapy in clinical settings, such as in patients with cancer and severe liver failure, a lack of substantial evidence has forced clinicians to rely mainly on anecdotal case reports. Furthermore, these case reports are scarce.

Quidde *et al* reported a literature review of 26 cases of secondary hyperbilirubinemia due to liver metastasis in patients with gastrointestinal cancer in 2016 (10). Among the 26 cases included, only one case of GC was documented, and the remaining 25 cases were of colorectal cancer. Of patients other than those with GC, 18 received chemotherapy, including oxaliplatin, and seven were treated with cetuximab monotherapy. In the report by Shitara *et al*, seven patients treated with cetuximab monotherapy exhibited good tolerance to the treatment, but the median overall survival was unsatisfactory at 2.8 months (11). Hwang *et al* reported a single case of GC treated with CapeOX, which exhibited hyperbilirubinemia due to multiple liver metastases. The total bilirubin decreased from 10.9 to 2.1 mg/dl after two cycles of CapeOX therapy, with no grade 3 or higher adverse effects during the first four cycles (12). For most of the other reported colorectal cancer cases, FOLFOX therapy was administered, with 13 out of 17 (one case with missing data) exhibiting a decrease in total bilirubin levels by over 50% compared with pre-treatment levels. No Grade 3 or higher adverse effects were reported. Based on these findings, Quidde *et al* concluded that regimens including oxaliplatin and 5-FU might be promising for patients with gastrointestinal cancer and liver failure.

Reports on the use of ICIs in patients with cancer and severe liver failure are scarce. Only two published cases exist: One involving the treatment of Hodgkin lymphoma with severe liver failure and encephalopathy using nivolumab monotherapy and another using pembrolizumab, cisplatin, and pemetrexed combination therapy to treat non-small cell lung cancer with multiple bile duct metastases, where bilirubin levels increased to 383 μmol/l (<20.5). In both cases, the ICIs were safely administered.

Kanz *et al* reported a multicenter retrospective analysis of treatment with nivolumab or pembrolizumab in patients with advanced cancer with impaired cardiac, renal, or hepatic function. Hepatic impairment in that study was defined as aspartate aminotransferase, alanine transaminase, and/or total bilirubin ≥3 times the upper limit of normal. Among the 27 analyzed patients, seven had hepatic function impairment, and four had liver cirrhosis. Notably, none of the patients had life-threatening encephalopathy or acute liver failure (6).

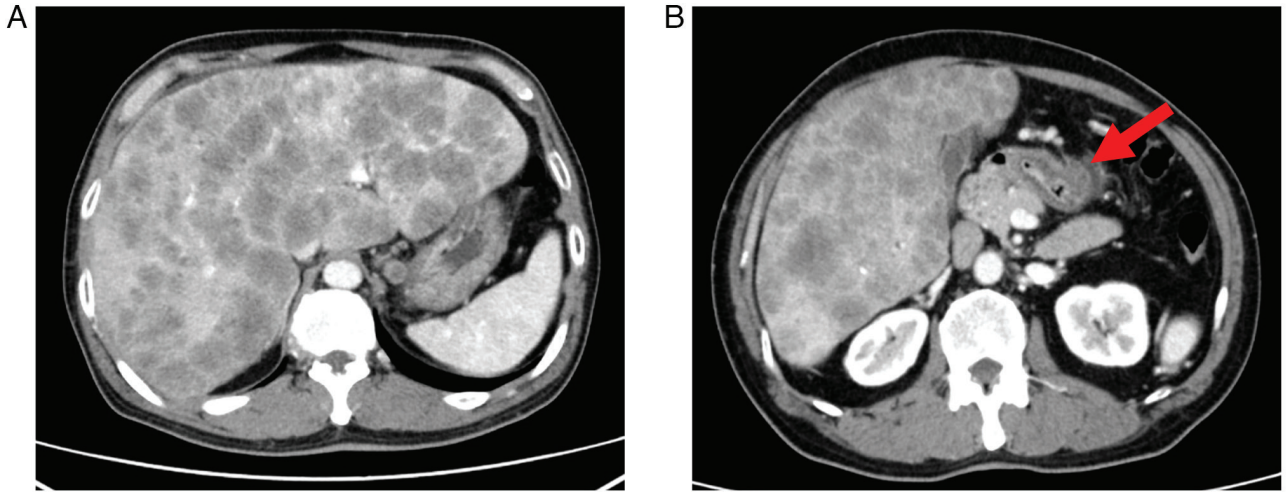

Figure 1. Computed tomography scan of the abdomen. (A) Multiple variable-sized metastatic nodular lesions are observed in the entire liver. (B) Thickening of the gastric pylorus wall is shown (red arrow).

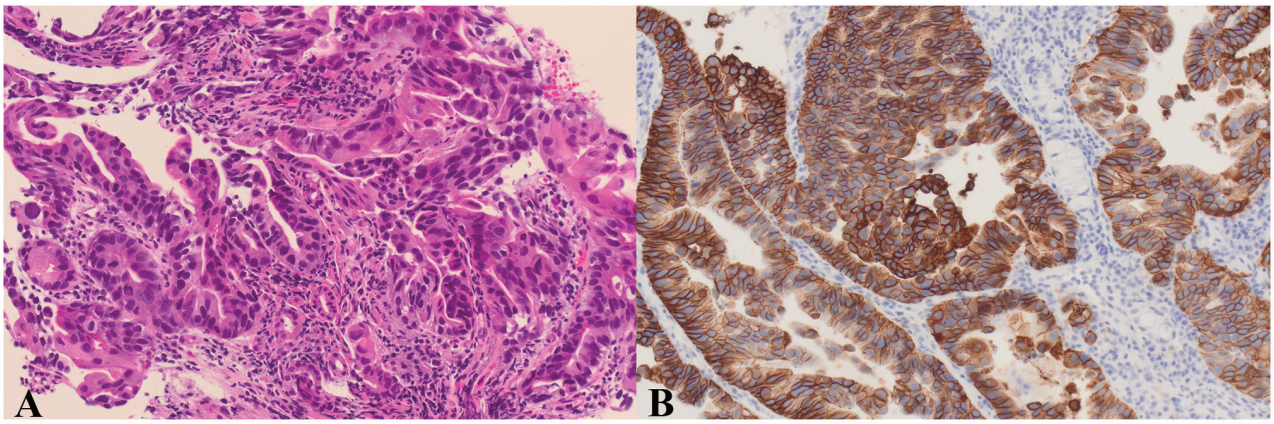

Figure 2. Pathological assessment of gastric mucosal specimens revealed the following: (A) Hematoxylin-eosin staining showed the presence of nuclear pleomorphism with enlarged and irregularly shaped nuclei. The tumor cells forming glandular structures infiltrate the surrounding tissue (magnification, x200). (B) Immunohistochemical staining demonstrated positive expression of HER2 in the tumor cells (magnification, x200).

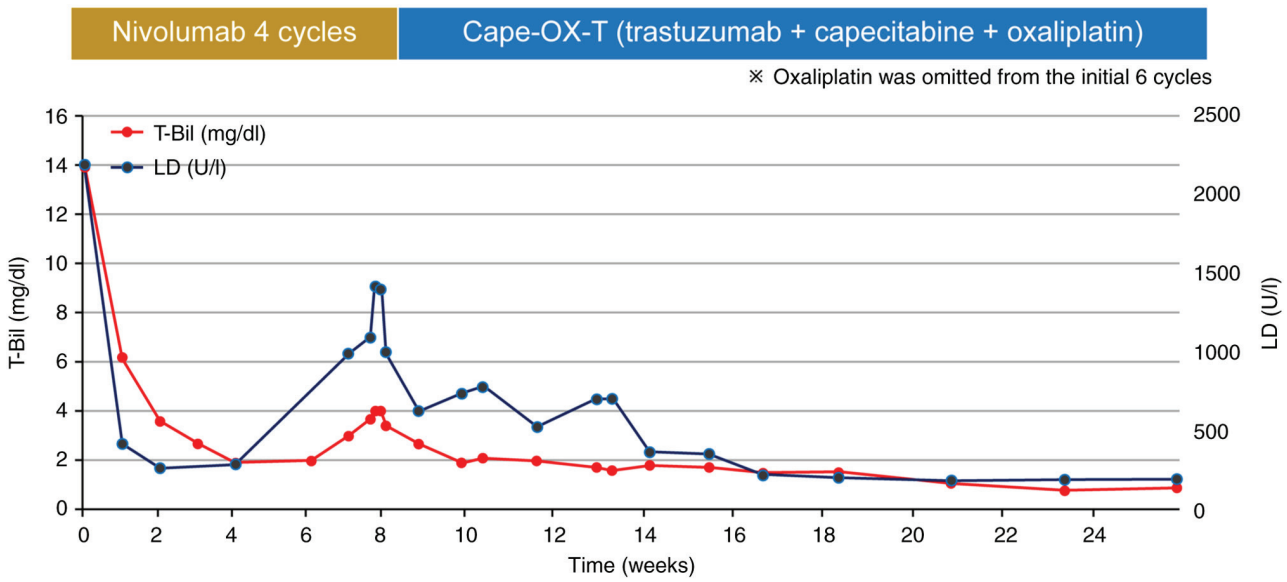

Figure 3. The trend of T-Bil and LD over time. After the administration of nivolumab, both parameters temporarily showed improvement, but a deterioration was observed after four courses. Upon switching treatment, subsequent improvements in the values were achieved. T-Bil, total bilirubin; LD, lactate dehydrogenase.

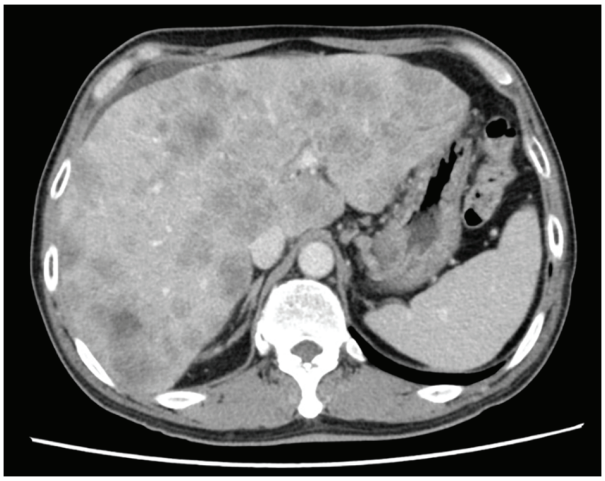

Figure 4. Computed tomography scan of the abdomen. A reduction in the size and a decrease in metastatic liver nodules after the fourth cycle of the nivolumab can be seen.

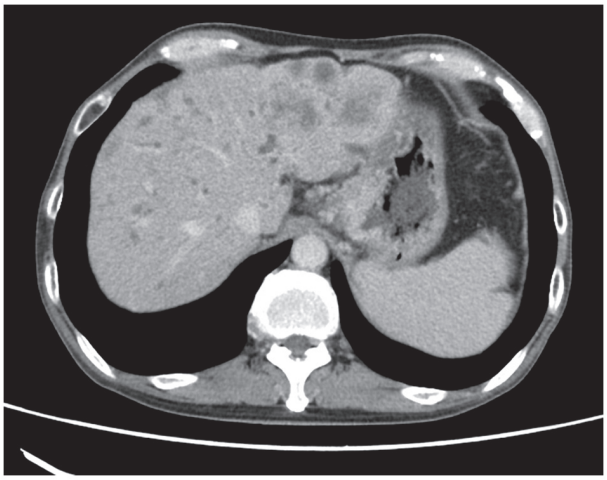

Figure 5. Computed tomography scan of the abdomen. A reduction in the size and a decrease in metastatic liver nodules after the tenth cycle of Cape-OX-T can be seen.

Zhao *et al* summarized the pharmacokinetics of ICIs administered to patients with liver and kidney impairment. They suggested that mild-to-moderate liver impairment requires no ICI dosage adjustments. However, in cases of severe liver impairment, ICIs have been administered only in two reported cases (13).

Herein, we present a case in which ICIs were safely administered to a patient classified as Child-Pugh class C with severe liver failure, resulting in prolonged survival. The prognosis for patients with gastrointestinal cancer and liver failure is typically speculated to be less than 3 months, as reported by Shitara *et al* (11). However, in this instance, the patient achieved a survival of 2 years and 6 months, significantly surpassing the 17.1-month median overall survival reported in the ToGA trial for the standard treatment of HER2-positive advanced GC, which includes trastuzumab, cisplatin, and capecitabine or fluorouracil therapy. Furthermore, the ToGA trial targeted patients with normal liver function and preserved organ capacity (14). To the best of our knowledge, this is the first study reporting a survival of 2 years and 6 months following targeted treatment in a patient with gastric cancer and severe liver failure. This observation suggests the possibility of therapeutic options for cases previously considered untreatable because of severe liver failure. We are aware of only one study (12) on the successful treatment of gastric cancer in patients with severe liver failure. However, this report only provides information up to the fifth session of chemotherapy (spanning a period of 2 and a half months). Most other studies have primarily focused on reports of liver metastases from colon cancer, with the most extensive case study being the report by Shitara *et al* (11). We believe this report is the most representative in this context. Additionally, to illustrate the general prognosis of inoperable HER2-positive gastric cancer patients without liver failure, we referenced literature (14). Our report shows an overall survival exceeding that of inoperable gastric cancer patients without liver failure documented in this literature.

In conclusion, documented cases involving ICI administration in patients with cancer and severe liver failure remain scarce. By accumulating additional insights, including the findings presented in this case, ICIs may solidify their position as a secure and efficacious therapeutic option even for instances of liver failure that complicate cancers previously considered incompatible for treatment with conventional chemotherapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FI, KY and KT participated in the conception, design and data acquisition of the study. FI drafted the manuscript. KY and KT revised the manuscript. FI and KT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient's wife, as the patient had passed away, for the case information and images to be published in this case report.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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