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Case Report

Rare Case of Advanced Gastric Cancer Complicated with Fibrinogen Storage Disease Treated with Chemotherapy plus Immune Checkpoint Inhibitor: A Case Report

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Keywords
Chemotherapy · Fibrinogen inclusion · Gastric cancer · Immune checkpoint inhibitor · Nivolumab

Abstract
The administration of chemotherapy to cancer patients with organ dysfunction raises concerns regarding its safety. The safety profile of patients with organ dysfunction due to rare diseases treated with chemotherapy plus immune checkpoint inhibitor is limited. Fibrinogen storage disease (FSD) is a rare disease that causes liver dysfunction through endoplasmic reticulum stress response due to abnormal accumulation of fibrinogen in the endoplasmic reticulum of hepatocytes. Although chemotherapy plus nivolumab is recommended as a standard first-line treatment for patients with advanced gastric cancer (AGC), its safety profile for patients with FSD is rarely available. In this study, an 80-year-old male with gastric cancer with positive lavage cytology was scheduled to receive palliative chemotherapy. This case had liver dysfunction of unknown cause, and a liver biopsy was performed. Histopathological findings revealed a diagnosis of type II/III fibrinogen inclusion based on morphology and immunohistochemistry. Liver function was recovered by administering ursodeoxycholic acid. Therefore, the combination chemotherapy of S-1, oxaliplatin, with nivolumab as palliative chemotherapy was initiated. The case responded well to chemotherapy and achieved conversion surgery without worsening of liver function. We report a case of AGC with fibrinogen inclusion complication where chemotherapy was safely administered with a good outcome. The combination therapy of cytotoxic drugs and immune checkpoint inhibitors may be safely and effectively administered to such patients.

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Introduction

In recent years, the CheckMate-649 trial showed that a combination of chemotherapy with nivolumab for patients with advanced gastric cancer (AGC) prolonged progression-free survival and overall survival compared with conventional standard therapy [1]. In addition, the ATTRACTION-4 trial revealed the nivolumab plus chemotherapy significantly prolonged progression-free survival compared to chemotherapy [2]. Currently, the combination therapy of fluoropyrimidines plus platinum agents and nivolumab is the recommended first-line treatment for human epidermal growth factor receptor 2 (HER2)-negative unresectable advanced or recurrent gastric cancer [3, 4].

When administering cytotoxic drugs with or without immune checkpoint inhibitors (ICIs) to patients with organ dysfunction, this could occur during chemotherapy; hence, it is necessary to carefully consider their indications. In particular, there may be concerns about the administration of these agents to patients with moderate to severe liver dysfunction. Although liver dysfunction is generally caused by various factors such as drugs, infection, or others, fibrinogen storage disease (FSD) has been reported as a rare underlying disease [5]. Fibrinogen is a glycoprotein that is synthesized in the liver as a blood coagulation factor and is then converted to fibrin by the action of thrombin to perform the functions of hemostasis, blood clotting, and thrombus formation. The main pathogenesis of FSD could be related to the abnormalities in its structure and/or function that result in its abnormal accumulation in the endoplasmic reticulum of the liver [6]. The degree of liver dysfunction varies from asymptomatic to severe impairment and even cirrhosis, and coagulopathy and bleeding tendencies are rare [5]. Although there is no established treatment available to date, ursodeoxycholic acid (UDCA) and carbamazepine have been reported as a treatment for liver dysfunction with FSD [7]. UDCA is effective in liver dysfunction as it inhibits endoplasmic reticulum stress caused by the accumulation of misfolded proteins and induces apoptotic signaling [8].

The safety profile of patients with organ dysfunction due to FSD treated with chemotherapy plus immune checkpoint inhibitor is limited. Herein, we experienced a case of unresectable AGC complicated with FSD that was safely and effectively treated with cytotoxic anticancer agents and ICIs. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534145).

Case Presentation

An 80-year-old male patient with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 had melena and anemia (case timeline presented in Table 1). Upper gastrointestinal endoscopy revealed a 1/2 circumferential Borrmann type 3 lesion at the lower gastric body to the anterior wall of the pylorus. The pathological finding was moderately differentiated adenocarcinoma. CT scan revealed bulky regional lymph node metastases (shown in Fig. 1), and the patient was diagnosed with clinical stage IIIC (cT4aN3M0) gastric cancer by TNM classification 8th edition and was referred to our hospital. After staging laparoscopy revealed P0CY0, laparoscopic gastric jejunal bypass surgery was performed due to the presence of intestinal obstruction. The cancer board decided to administer neoadjuvant chemotherapy because of the presence of bulky N, and the patient was referred to our department. However, liver dysfunction was detected on the day of treatment through blood tests (AST, 186 U/L; ALT, 178 U/L; γ-GTP, 74 U/L; and ALP, 163 U/L). The patient had no history of heavy drinking or suspected medications. Antinuclear antibodies,

Table 1. Case timeline

X/08	Diagnosed gastric adenocarcinoma(cT4aN3M0) with pyloric stenosis.
X/09	Performed laparoscopic gastric jejunal bypass surgery.
X/10	Referred to our division. Liver dysfunction was emerged.
X/11	Liver biopsy revealed fibrinogen storage disease.
X/12	Initiation of chemotherapy.
X+1/5	RECIST PR was confirmed.
X+1/7	Conversion surgery was performed.

antimitochondrial antibodies, and hepatitis viral markers were negative, with no elevation of IgG levels. Abdominal ultrasonography and CT scan did not show any abnormal findings. Liver dysfunction did not improve to levels that would allow chemotherapy to be safely administered. Hence, upfront surgery was planned for the patient. However, staging laparoscopy revealed P0CY1; therefore, the patient was scheduled to receive palliative chemotherapy. Since liver dysfunction continued, a liver biopsy was performed that showed hepatocytes with eosinophilic round inclusion bodies (shown in Fig. 2a). The inclusion bodies were positive for fibrinogen immunostaining (shown in Fig. 2b) and C-reactive protein (CRP) immunostaining (shown in Fig. 2c), whereas they were negative for PAS staining (shown in Fig. 2d). Since serum fibrinogen level was within normal limits, we finally diagnosed the patient as type II/III FSD. Because liver function recovered after administering UDCA, the combination therapy of S-1 plus oxaliplatin (SOX) with nivolumab was initiated based on the results of immunohistochemical staining for programmed cell death 1 (PD-L1 combined positive score 10). Considering age, oxaliplatin was reduced by two levels (85 mg/m^2) and S-1 was reduced by one level (100 mg/day). After four courses of treatment, a CT scan revealed tumor shrinkage, and the patient was determined to be RECIST PR. After seven courses of SOX plus nivolumab, RECIST PR was confirmed. A deep response was achieved, and R0 resection was considered feasible. Therefore, the decision to perform conversion surgery was made. Treatment-related adverse events included grade 2 peripheral neuropathy and dermatitis grade 1. Hepatic enzymes did not elevate during treatment with SOX plus nivolumab.

Discussion

FSD is a liver disorder characterized by abnormal fibrinogen accumulations in the endoplasmic reticulum of hepatocytes, causing an endoplasmic reticulum stress response [9]. FSD is classified into three groups (type I, type II, and type III) based on differences in the form of fibrinogen that abnormally accumulates. Type I is inherited in an autosomal dominant manner with mutations in the fibrinogen gamma chain [10], whereas type II and type III are nonhereditary and are caused by acquired intracellular secretory dysfunction due to infection or other agents [6]. Pathologically, type I inclusions are characterized by irregularly contoured

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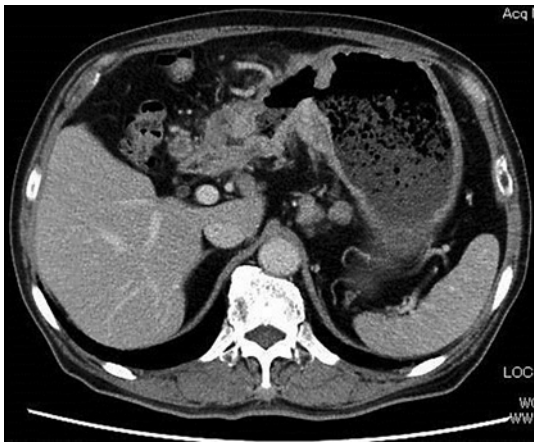

Fig. 1. CT abdominoplasty. CT scan at the initial examination: wall thickening was observed in the gastric horn to pyloric anterior wall kyphosis. The pyloric region was narrowed by the tumor, and the stomach was dilated at the mouth. Multiple enlarged lymph nodes were observed around the greater and lesser curvatures of the stomach.

circular to polygonal inclusions; type II, by large, single, frosted, glass-like inclusions; and type III, by circular inclusions with halos [10, 11]. Type II and type III can coexist in the same case. All types have fibrinogen-positive hepatocyte inclusions. In addition, the inclusion bodies are negative or weakly positive for PAS staining, and type II/III inclusion bodies can be positive for proteins such as C3, C4, and CRP [6, 11]. In our case, the inclusion body observed was acidophilic and round, with a mixture of large single inclusions and inclusions with halos. This morphology was consistent with type II/III FSD. The inclusion body was positive for fibrinogen immunostaining and CRP staining, and hence, a diagnosis of type II/III FSD was made. Considering the age of onset, patient background, pathological findings described above, and normal serum fibrinogen levels, it was suggested that the disease might have been acquired. There was no history showing the onset of FSD, and there have been no previous studies reporting its association with gastric cancer. Therefore, the causal relationship between gastric cancer and FSD is unknown.

High response rates have been reported with ICI combination therapy in various tumors; however, immunotherapy has limited efficacy for gastric cancer, and, hence, it is important to understand the association with biomarkers [1, 2, 12]. Patients with unresectable AGC generally require systemic therapy and the appropriate regimen is decided based on HER2 status, microsatellite instability status, and PD-L1 expression [13]. In this case, the patient had a CPS score of 10, and we considered the possibility that the patient received a deep response to the ICI combination therapy. Immunotherapy provided longer term responses in chemotherapy for cancer patients, and deeper response has been achieved in an increasing number of cases.

Generally, adequate organ function should be preserved at the initiation of chemotherapy, and moderate to severe liver dysfunction requires appropriate dose reductions. Oxaliplatin, a key drug in chemotherapy for AGC, is known to cause liver dysfunction by destroying hepatic sinusoidal endothelial cells, resulting in sinusoidal narrowing and stagnation of blood flow [14]. Nivolumab also causes hepatitis as an immune-related adverse event by activating T cells and damaging normal hepatocytes [15]. The frequency of grade 3 or higher liver dysfunction in chemotherapy and nivolumab is approximately 1% [1, 2]. Therefore, it is considered that chemotherapy could be relatively safely administered. In case of liver dysfunction grade 2 or more, the combination therapy of a cytotoxic anticancer agent with nivolumab often requires steroid treatment even after drug cessation in case of suspected immune-related adverse event. In this case, FSD-induced liver dysfunction was controlled with UDCA, and chemotherapy administration was considered feasible. There are no previous reports on the safety of cytotoxic anticancer agents with or without ICIs for patients with

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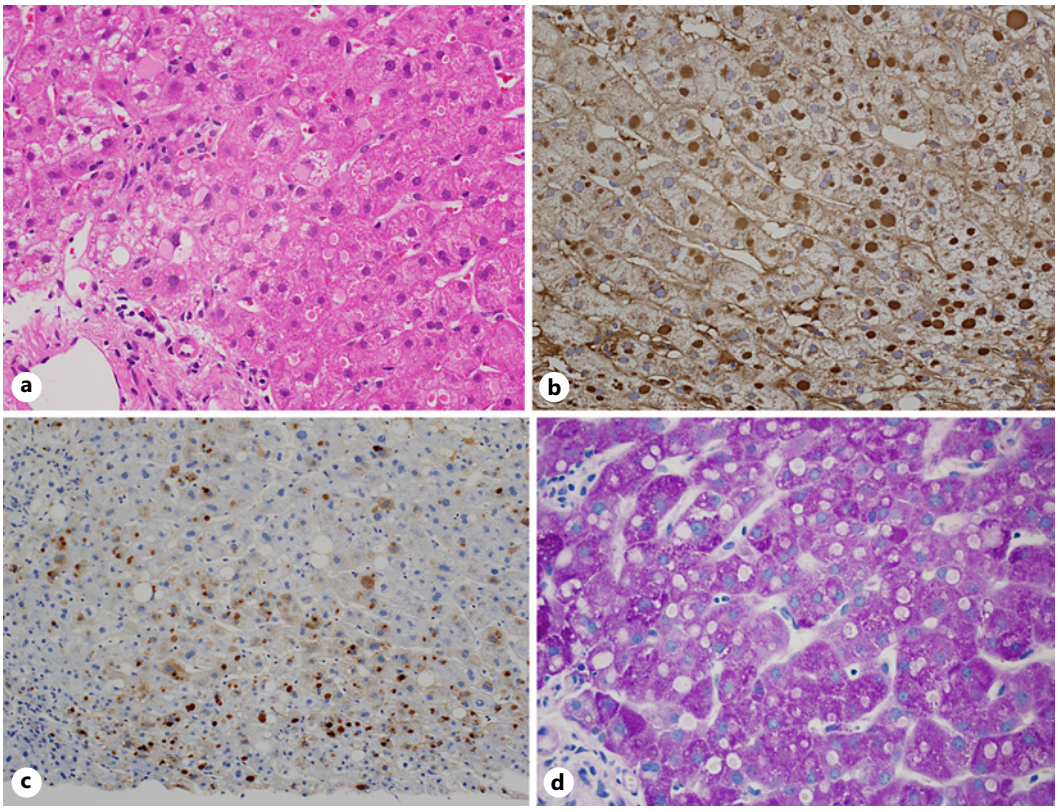

Fig. 2. Histopathology of liver biopsy. **a** H&E staining (×40): most hepatocytes had pale acidophilic, rounded inclusion bodies. **b** Fibrinogen immunostaining (×40): inclusion bodies showed positive fibrinogen immunostaining. **c** CRP immunostaining: inclusion bodies showed positive CRP immunostaining. **d** PAS staining (×40): the inclusion bodies are negative for PAS staining, and there was no glycogen within the inclusion bodies.

advanced solid tumors complicated with FSD. In this case, liver dysfunction did not occur and careful monitoring of transaminases was considered necessary. The treatment duration of SOX plus nivolumab was approximately 6 months, and the patient received no further treatment with chemotherapy to achieve deep tumor shrinkage and successfully underwent the conversion surgery. There is a possibility of new adverse events emerging, requiring careful monitoring if long-term treatment is needed. After 18 months of chemotherapy, the health of the patient was fine and new adverse events are not reported.

Conclusion

SOX plus nivolumab for patients with unresectable AGC complicated with FSD could be safely administered as long as liver function is controlled. The patient received chemotherapy for 6 months only, and more such case studies are needed to determine the safety of its long-term treatment.

Acknowledgment

We thank the patient for providing consent to publish this case report.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Takeshi Kawakami received honoraria from Ono Pharmaceutical and Bristol Myers Squibb. Kentaro Yamazaki received honoraria from Chugai Pharma, Daiichi Sankyo, Yakult Honsha, Takeda, Bayer, Merck Serono, Taiho Pharmaceutical, Lilly, Sanofi, Ono Pharmaceutical, MSD, and Bristol Myers Squibb, and funding from Taiho Pharmaceutical.

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Author Contributions

D.K. drafted and edited the manuscript. T.K. was involved in patient management. Y.K. performed the histopathological analysis. T.K. and K.Y. were involved in the final revision of the manuscript and coordinated the submission. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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