

A Patient with a Large Gastric Tumor and Protein-Losing Gastroenteropathy Successfully Treated with Neoadjuvant TS-1 Combined with CDDP Therapy

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Key Words

Gastric cancer · Protein-losing gastroenteropathy · Neoadjuvant chemotherapy

Abstract

Gastric cancer with protein-losing gastroenteropathy is relatively rare worldwide. The most important problem for the treatment of these patients is their low nutritional status and protein level, which can cause severe postoperative complications. We report a 49-year-old Japanese female with a large gastric tumor and protein-losing gastroenteropathy successfully treated with neoadjuvant TS-1 combined with CDDP therapy. She had a type 5 tumor with partially cauliflower-like appearance. Her blood chemistry revealed low serum total protein (3.3 g/dl) and low albumin (1.7 g/dl). She was additionally diagnosed with protein-losing gastroenteropathy based on ^{99m}Tc-human serum albumin scintigraphy. Initial neoadjuvant chemotherapy decreased the size of the tumor and led to a marked improvement in her serum protein levels. She then underwent a total gastrectomy and lymph node dissection (D2) with a combined resection of the spleen and gallbladder. Therefore, neoadjuvant chemotherapy may provide a safe treatment before definitive surgery for gastric cancer with protein-losing gastroenteropathy.

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Introduction

Protein-losing gastroenteropathy was first reported by Kimbel et al. [1] in 1956. This syndrome is associated with excessive loss of plasma protein into the gastrointestinal tract, which can be complicated by edema, ascites, pleural and pericardial effusion and malnutrition [2]. Gastric cancer with protein-losing gastroenteropathy is relatively rare. The most important problem in treating gastric cancer patients with protein-losing gastroenteropathy is their low nutritional status and protein level. This makes it difficult to determine the indications for surgery and may cause severe postoperative complications. Therefore, we used the Prognostic Nutritional Index (PNI) [3] for predicting the incidence of postoperative complication. The PNI is a simple and useful index calculated using the levels of serum albumin and total lymphocyte count in the peripheral blood. We herein report a patient with advanced gastric cancer with protein-losing gastroenteropathy successfully treated with neoadjuvant TS-1 combined with CDDP therapy.

Case Report

A 49-year-old woman visited the Department of Gastroenterological Surgery, Fukuoka University School of Medicine, due to the presence of severe edema in both legs, weight loss and anorexia. On upper gastrointestinal endoscopy, we observed a type 5 tumor with a partially cauliflower-like appearance (fig. 1a). Biopsy specimens from the tumor revealed a poorly differentiated adenocarcinoma. Her blood chemistry showed low total serum protein (3.3 g/dl), albumin (1.7 g/dl), total lymphocyte count (1,706 μ l), and red blood cell count (11.4 g/dl). Her PNI value was 24.6. She had no diagnosis of heart, renal or liver disease. An abdominal contrast computed tomography scan showed the primary cancer to be located in the gastric body and to have metastasized to the perigastric lymph nodes. A mild ascites in the pelvic cavity was also detected. Upon performing a staging laparoscopic examination, we did not observe peritoneal dissemination or malignancy in the cytology of the ascites. However, a 99m Tc-human serum albumin scintigraphy revealed a significant loss of protein into the gastrointestinal tract (fig. 2a). Based on these findings, the patient was diagnosed with gastric cancer with protein-losing gastroenteropathy. According to the Japanese classification [4], the clinical stage of gastric carcinoma was cT3(SS) N1 P0 H0 CY0 M0: cStage IIIA.

Because her nutritional status and PNI value were very low, we recommended that she receive neoadjuvant chemotherapy before definitive surgery. S-1 (100 mg/body per day) was given orally for 3 weeks on a 5-week cycle. CDDP (60 mg/m²) was administered intravenously on the 8th day after starting chemotherapy [5, 6]. The patient received 2 cycles of this regimen. After chemotherapy, her blood chemistry improved in serum total protein (4.9 g/dl), albumin (3.2 g/dl), total lymphocyte count (1,776 μ l), and red blood cell count (10.9 g/dl). Her PNI value increased to 41.0. After performing an upper gastrointestinal endoscopy, we observed a decrease in the size of the primary tumor (fig. 1b). Furthermore, we did not detect a loss of protein in the gastrointestinal tract using 99m Tc-human serum albumin scintigraphy after chemotherapy (fig. 2b).

We performed a total gastrectomy and lymph node dissection (D2) with a combined resection of the spleen and gallbladder. Resected specimens showed a polypoid tumor with a well-demarcated depressed lesion (approximately 8.0 cm in diameter) in the upper-middle part of the stomach (fig. 3a, b). Histologically, the tumor was composed of poorly to well-differentiated adenocarcinoma. The tumor invaded the submucosal tissue (pT1b2) with

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minimal lymphatic invasion (fig. 3c, d). We did not detect metastatic foci of adenocarcinoma in the regional lymph nodes. Tumor classification after preoperative chemotherapy was ypT1b2 N0 P0 H0 CY0 M0: ypStage IA.

The postoperative course was uneventful and the patient was discharged 20 days after surgery with no complications. Her serum total protein and albumin levels normalized, and the edema in both legs disappeared. Adjuvant chemotherapy was not administered.

Discussion

Protein-losing gastroenteropathy is a syndrome associated with excessive loss of plasma protein into the gastrointestinal tract. This syndrome is caused by various disorders such as digestive diseases, collagen diseases or cardiac diseases [7]. The main underlying mechanism of protein-losing gastroenteropathy is lymphatic or mucoepithelial abnormalities of the gastrointestinal tract or increased vascular permeability [8, 9]. In gastrointestinal cancer, protein-losing gastroenteropathy is caused by lymphatic vessel dilatation resulting from the obstruction of these vessels by cancer cells or proteins they produced [10].

A case of gastric cancer with protein-losing gastroenteropathy was first reported in the English literature in 1964 by Sum et al. [11], and to the best of our knowledge, only 3 additional English cases have been reported [10–12]. Twenty-nine cases of gastric cancer with protein-losing gastroenteropathy have been reported in the Japanese literature, most likely due to the fact that Japan has a higher occurrence of gastric cancer [13]. Among the 32 cases with detailed information [10, 12, 14] (including ours), 56.2% of patients were male with a mean age of 75.1 years. The chief complaint from these patients was edema of the limbs (90.6%), especially in the legs. Macroscopic findings showed that most tumors were large (average diameter of 10.1 cm) and had a cauliflower-like or villous appearance (82.6%). However, only 41.4% of the cases of gastric cancer in patients with protein-losing gastroenteropathy were classified as advanced. Protein-losing gastroenteropathy was diagnosed by either ^{99m}Tc-human serum albumin scintigraphy or an α_1 -antitrypsin clearance test [15, 16]. Of all these published cases, ours is the first to report a decrease in protein loss into the gastrointestinal tract by ^{99m}Tc-human serum albumin scintigraphy after chemotherapy treatment for gastric cancer.

The most important problem for the treatment of gastric cancer in patients with protein-losing gastroenteropathy is their low nutritional status and protein level. This can cause severe postoperative complications such as anastomotic leakage and surgical site infections. Onodera et al. [3] reported PNI as a simple index calculated using the levels of serum albumin and total lymphocyte count in the peripheral blood to predict the incidence of postoperative complications. A lower PNI value is associated with a higher incidence of postoperative complications. Resection and anastomosis of the gastrointestinal tract can be safely performed only when the PNI value is over 45. This procedure can be dangerous in patients with PNI values between 45 and 40, and contraindicated in patients with values below 40.

Our patient's PNI value was 24.6 when she first arrived at our hospital. Therefore, we explained to her that surgery in her condition could be dangerous, with risks of postoperative complications. She therefore chose to receive neoadjuvant chemotherapy before definitive surgery. TS-1 combined with CDDP therapy is the recommended regimen for Japanese patients with unresectable or recurrent gastric cancer, based on the results of the SPIRITS trial [5]. Neoadjuvant chemotherapy for gastric cancer has not yet been established in Japan. However, a randomized phase III trial for type 4 and large type 3 gastric cancer

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comparing surgery plus neoadjuvant TS-1 and cisplatin with surgery alone is now ongoing (JCOG 0501).

In conclusion, gastric cancer with protein-losing gastroenteropathy is relatively rare. It is difficult to determine the surgical indications for patients with low nutritional status and protein level as these may cause severe postoperative complications. Therefore, neoadjuvant chemotherapy may safely reduce the effects of protein-losing gastroenteropathy in these patients, which will then allow them to undergo surgery.

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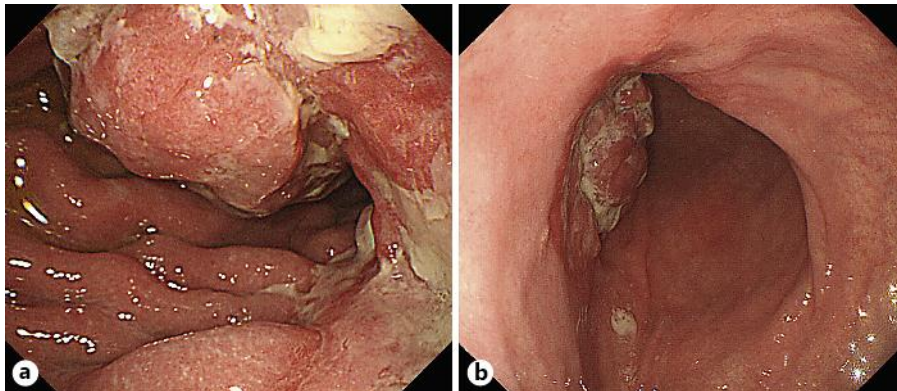


Fig. 1. **a** Upper gastrointestinal endoscopy demonstrated a type 5 tumor with a partially cauliflower-like appearance. **b** Upper gastrointestinal endoscopy demonstrated a decrease in the size of the primary tumor after chemotherapy.

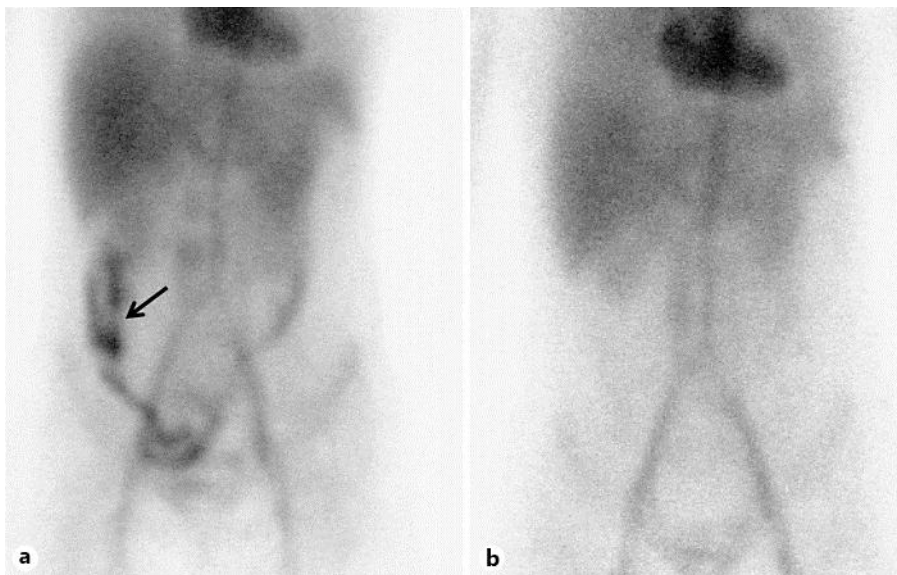


Fig. 2. **a** ^{99m}Tc -human serum albumin scintigraphy showed a hot spot that depicts a significant loss of protein into the gastrointestinal tract (arrow). **b** The loss of protein into the gastrointestinal tract was not detected on ^{99m}Tc -human serum albumin scintigraphy after chemotherapy.

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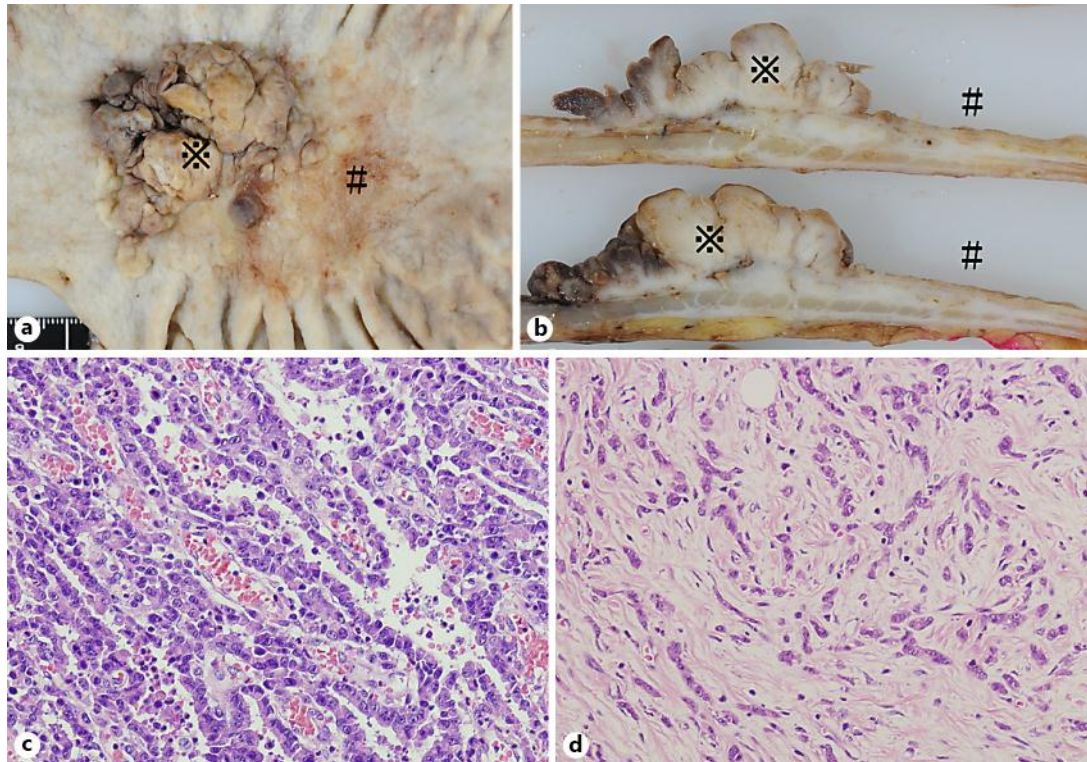


Fig. 3. Macroscopic and histological features of the resected specimen. **a** A polypoid tumor (✕) with a well-demarcated depressed lesion (#) is located in the upper-middle part of the stomach. **b** The cut surface of the tumor shown in **a**. **c** The superficial zone of the intramucosal lesion is composed of well-differentiated adenocarcinoma. **d** Submucosal tissue in the gastric wall, showing infiltrating growth with stromal fibrosis.