Late recurrence of CD44 variant 9-positive gastric carcinoma 12 years after surgery: A case report

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Case Report

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Abstract

Background

Late recurrence of gastric cancer of over 10 years post-gastrectomy is extremely rare, and the mechanism of late recurrence is unclear. We report a case of para-aortic lymph node metastasis that recurred 12 years postoperatively.

Case presentation

A 44-year-old woman who was pathologically diagnosed with moderately to poorly differentiated adenocarcinoma with T2N2M0 Stage IIIA according to the Japanese Classification of Gastric Carcinoma (the 13th Edition) underwent laparoscopic distal gastrectomy with D1 + lymph node dissection. She received adjuvant chemotherapy with tegafur-uracil (400 mg/day) for 2 years. At postoperative year (POY) 5, a swollen lymph node was detected in the No.16b1lat lymph node station. However, positron emission tomography (PET) revealed normal uptake, and tumor markers were within normal limits; hence, the possibility of metastasis was judged to be low, and the patient was placed under observation. At POY 12, computerized tomography revealed an enlargement of the No.16b1lat lymph node station, and PET revealed abnormal uptake. Endoscopic ultrasound-guided fine-needle aspiration revealed a moderately differentiated adenocarcinoma. Hence, a diagnosis of recurrence of gastric cancer was made. She underwent para-aortic nodal dissection (PAND) of No.16b1lat & int stations. Immunochemical staining was similarly consistent with recurrence of gastric cancer. Meanwhile, CD44 variant 9 (CD44v9), a cancer stem cell marker for gastric adenocarcinoma, was attenuated in the recurrent lesions compared with the primary lesions. Postoperatively, she received chemotherapy with tegafur-gimeracil-oteracil (80 mg/day) for 1 year. At POY 4 after PAND, the patient remained well with no evidence of recurrence and distant metastasis.

Conclusions

The degree of staining for CD44v9 in the recurrent lesions may be related to the timing of recurrence. Hence, it is important to continue to investigate the role of the expression of CD44v9 in gastric cancer and to clarify the details.

Background

Gastric cancer is the fifth most common cancer worldwide and the third most common cause of cancer-related mortality.(1) In gastric cancer, metastasis and recurrence are refractory to treatment, leading to a poor prognosis. Although clinical stage, tumor size, depth of invasion, and lymph node metastasis are known prognostic factors for early recurrence, no independent risk factor has been identified for late recurrence of over 10 years after surgery.(2–4) Local recurrence, lymph node metastases, and liver
metastases occur within 3 years postoperatively, while peritoneal dissemination and other hematogenous metastases occur within 5 years postoperatively. Thus, late recurrence at 10 years after gastrectomy is extremely rare. Herein, we report a case of para-aortic lymph node metastatic recurrence 12 years after surgery.

**Case Presentation**

A 44-year-old woman presented to our hospital with a 1-month history of appetite loss. A barium study and endoscopic examination revealed type 3 gastric cancer with a pathologic diagnosis of moderately differentiated adenocarcinoma, in the lesser curvature of the gastric angle. Contrast-enhanced computed tomography (CT) revealed no lymph node swelling or distant metastasis. Her serum carcinoembryonic antigen (CEA) level was 0.6 ng/mL, and her carbohydrate antigen 19 − 9 (CA19-9) level was 9.6 ng/mL. The preoperative diagnosis was T2(MP)N0M0StageIB (Japanese Classification of Gastric Carcinoma [The 13th Edition]). She underwent laparoscopic distal gastrectomy (D1+) + Roux-en-Y reconstruction. Histopathologic examination of the surgical specimen revealed superficial extension of moderately to poorly differentiated adenocarcinoma, and partial invasion of the serous membrane (T2:SS). Severe lymphatic invasion (ly3), moderate venous invasion (v2), and lymph node metastases in No.1,3,7, and 9 lymph node stations (N2) were observed. The postoperative diagnosis was T2(SS)N2M0StageIIIA (Japanese Classification of Gastric Carcinoma [The 13th Edition]) (Fig. 1). The patient received adjuvant chemotherapy with tegafur-uracil (400 mg/day) for 2 years. Blood tests including tumor markers and a whole-body CT were performed every 3 months and 6 months, respectively. Endoscopic examination was conducted at least annually. At postoperative year (POY) 5, a 19 × 12-mm lymph node was detected in the No.16b1lat lymph node station (Japanese Classification of Gastric Carcinoma [The 13th Edition]) (Fig. 2a). However, positron emission tomography (PET) revealed no abnormal uptake, and the tumor markers were within normal limits (CEA, 1.3 ng/mL; CA19-9, 20.3 U/mL) (Fig. 2b); hence, the possibility of metastasis was judged to be low, and the patient was placed under observation. Although no increase in size was noted, the patient was followed up with annual whole-body CT, and the tumor markers remained within normal limits. At POY 10, blood examination revealed that the CA19-9 level was elevated to 39.2 U/mL, although no increase in size was noted. At POY 12, the No.16b1lat lymph node station enlarged to 30 × 15 mm, the PET revealed abnormal uptake in the same lesion, and the CA19-9 level was further elevated to 72.6 U/mL (Fig. 3a, b). No other tumor was noted during esophagogastroduodenoscopy and colonoscopy. Endoscopic ultrasound-guided fine needle aspiration revealed a moderately differentiated adenocarcinoma, similar to the histology of the previous surgery specimen; hence, a diagnosis of recurrence of gastric cancer was made. After two cycles of chemotherapy with tegafur-gimeracil-oteracil (120 mg/day) + oxaliplatin (100 mg/m²), the recurrent lesion decreased in size to 18×9 mm (RECIST: PR; partial response), and tumor marker levels also decreased (CEA: 1.1 ng/mL, CA19-9: 20.3 U/mL). Para-aortic nodal dissection (PAND) of No.16b1lat & int stations was performed. In the dissected lymph nodes, a proliferative image of adenocarcinoma cells demonstrated conjoined tubular structures, a finding consistent with gastric cancer metastasis (Fig. 4a). Around the adenocarcinoma cells, scar-like fibrosis and aggregation of foamy histiocytes were observed, indicating that a part of the tumor disappeared...
because of chemotherapy. The immunohistochemical staining showed that CK7 was expressed both in primary and recurrent specimens (Fig. 1c, 4b). The immunohistochemical staining for CK20 was not expressed in primary and recurrent specimens (Fig. 1d, 4c). Based on these immunohistochemical findings, a diagnosis of recurrence of gastric cancer was made. Postoperatively, the patient received chemotherapy with tegafur-gimeracil-oteracil (80 mg/day) for 1 year. At POY 4 after PAND, the patient is alive with no evidence of recurrence and distant metastasis.

**Discussion And Conclusions**

We encountered a case of a late recurrence of gastric cancer at POY 12. The histopathological findings were useful in confirming the diagnosis of postoperative recurrence of gastric cancer. The histology of the recurrent tumor indicated proliferation of adenocarcinoma cells, similar to the histology of the previous surgical specimen. Gastric adenocarcinoma demonstrated either a CK7 or CK20 expression pattern; the recurrent lesion was CK7 positive/CK20 negative, consistent with the primary lesion. No epithelial tumor was detected by esophagogastroduodenoscopy and colonoscopy, and other cancers were not suspected by contrast-enhanced CT and PET. These findings further support the diagnosis of recurrence of gastric cancer.

To consider the reasons for late recurrence, we investigated the expression of CD44 variant 9 (CD44v9) with immunohistochemical staining. CD44 is a marker for cancer stem cells (CSCs) found in various solid tumors such as breast, colon, and gastric cancers. It is a major adhesion molecule in the extracellular matrix. CSCs have been defined as a unique subpopulation in tumors that possess the ability to initiate tumor growth and sustain tumor self-renewal. CD44 gene transcripts undergo complex alternative splicing, among which CD44v9 expression is significantly associated with a poor prognostic factor for overall and recurrence-free survival. CD44v9 stabilizes the glutamate–cystine transporter and promotes the uptake of cystine, which is required for glutathione (GSH) synthesis in the cell. GSH is the most abundant non-enzymatic antioxidant molecule in cells and acts directly in the removal of intracellular reactive oxygen species (ROS). Glutathione peroxidase 2, the gastrointestinal form of glutathione peroxidase, is an antioxidant enzyme that catalyzes the reduction of intracellular ROS using GSH as a reductant. This defense mechanism against ROS prevents apoptosis of CSCs, making them resistant to anticancer drug therapy and radiotherapy. Conversely, silencing CD44v9 with siRNA has been reported to promote apoptosis and cell cycle arrest and inhibit cell proliferation. In our case, the expression of CD44v9 was attenuated in the recurrent lesion compared to the primary lesion (Fig. 5a, b). The defense mechanism against ROS in the recurrent lesion may be weakened in combination with the decreased expression of CD44v9. In contrast, the number of CD44v9-positive cells is low, tumor formation and cell proliferation may also be suppressed. The antagonistic speed of cell proliferation and apoptosis may contribute to the inhibition of tumor growth. Meanwhile, Ki-67 labeling index of less than 3% (Fig. 1e, 4d) and the weak accumulation of FDG by PET suggest that the tumor cells are in a state of cell cycle arrest or dormancy. Thus, the expression of CD44v9 in recurrent lesions may cause late recurrence.
We hypothesized that there might be a correlation between the degree of CD44v9 expression in recurrent lesions and the timing of recurrence. We investigated the expression of CD44v9 in the primary and recurrent lesions in seven patients who underwent radical gastric cancer surgery and resection of recurrent lesions in our hospital. Among them, CD44v9 was positive in three cases. Case 1 was the present case of gastric cancer with para-aortic lymph node recurrence 12 years postoperatively, Case 2 was gastric carcinoma with para-aortic lymph node recurrence 5 years postoperatively, and Case 3 was esophagogastric junction carcinoma with skin metastasis 8 months postoperatively. The expression of CD44v9 was classified as primary/recurrence: positive/slightly positive in Case 1, positive/negative or unclear in Case 2, and positive/positive in Case 3. In Case 3 (early recurrence), high expression of CD44v9 in the recurrent lesion was strongly observed. We suspect that in gastric cancers expressing CD44v9, cases with a higher percentage of CD44v9 expression in the recurrent lesion have a shorter time to recurrence in contrast to those with a lower percentage of CD44v9 expression.

In conclusion, the degree of staining for CD44v9 in the recurrent lesions may be related to the timing of recurrence. As there are only few cases in which surgery for gastric cancer recurrence is indicated, and consequently, pathological findings in recurrent lesions are rarely reviewed, it is important to continue to investigate the role of the expression of CD44v9 in gastric cancer and to clarify the details.

**Abbreviations**

CA19-19, carbohydrate antigen 19 – 9

CD44v9, CD44 variant 9

CEA, carcinoembryonic antigen

CSCs, cancer stem cells

CT, computed tomography

GSH, glutathione

PAND, para-aortic nodal dissection

PET, positron emission tomography

POY, postoperative year

ROS, reactive oxygen species

**Declarations**

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Gifu University Hospital.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Availability of data and materials**


**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

HH drafted the manuscript. IY, TH, WC, RY, MF, YS, RA, JT, CS, AM, YT, NO, KM, TT, MF, TT, and NM provided academic advice. TH, WC, CS, and TT contributed to the pathological diagnosis. All authors read and approved the final manuscript.

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**References**


**Figures**

![Figure 1](image)

**Figure 1**

(a) The tumor presented in the lesser curvature of the gastric angle. (b) Histopathologic examination of the surgical specimen revealed superficial extension of intermediate to poorly differentiated adenocarcinoma, and partial invasion of the serous membrane. On immunohistochemical analysis, the tumor cells were positive for CK7 (c), negative for CK20 (d) and showed a Ki-67 labeling index of less than 3% (e).
Figure 2

At post-operative year 5, positron emission tomography/computerized tomography detected a 19 × 12 mm lymph node in the No. 16b1lat lymph node station with no abnormal uptake.

Figure 3

At post-operative year 12, positron emission tomography/computerized tomography detected a 30 × 14 mm lymph node in the No. 16b1lat lymph node station with abnormal uptake.
Figure 4

(a) Histopathologically, a proliferative image of adenocarcinoma cells demonstrated conjoined tubular structures. On immunohistochemical analysis, the tumor cells were positive for CK7 (b), negative for CK20 (c) and showed a Ki-67 labeling index of less than 3% (d).
Figure 5

Case 1 (the present case): gastric cancer that recurred in para-aortic lymph nodes 12 years postoperatively. The expression of CD44 variant 9 (CD44v9) as primary (a)/recurrence (b): positive/slightly positive.
Case 2: gastric carcinoma with para-aortic lymph node recurrence 5 years postoperatively. The expression of CD44v9 as primary (c)/recurrence (d): positive/negative or unclear.

Case 3: esophagogastric junction carcinoma with skin metastasis 8 months postoperatively. The expression of CD44v9 as primary (e)/recurrence (f): positive/positive.