

[CASE REPORT]

Recurrence of Cutaneous and Lymph Node Metastases 12 Years after Radical Total Gastrectomy for Stage IIA Gastric Cancer

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Abstract:

We herein report a rare case of cutaneous and lymph node metastases that recurred 12 years after radical total gastrectomy for stage IIA gastric cancer. A 62-year-old man had undergone total gastrectomy for stage IIA gastric cancer 12 years earlier without postoperative adjuvant chemotherapy. At 12 years after the surgery, he was admitted for left jugular swelling. Computed tomography revealed supraclavicular lymph node swelling and precordial subcutaneous edema. The lymph node specimens and cutaneous biopsies indicated late recurrence of the gastric cancer. Concurrent chemoradiotherapy was administered effectively, but after eight months, the patient died due to deterioration in his general condition.

Key words: gastric cancer, cutaneous metastases, late recurrence, radical total gastrectomy

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Introduction

The outcomes of postoperative gastric cancer are generally evaluated on the basis of the five-year survival rates. There have been only a few reports of gastric cancer with cutaneous metastases that recurred after >10 years.

We herein report a rare case of cutaneous and lymph node metastases that recurred 12 years after radical total gastrectomy for stage IIA gastric cancer, along with a literature review.

Case Report

A 62-year-old man was admitted to the hospital for left jugular swelling. He had a history of gastric cancer that had been diagnosed in the lesser curvature of the lower gastric body 12 years earlier (Fig. 1). He had no remarkable medical history except for the gastric cancer, and he was not taking any medications, nor did he have any allergies. He did not consume alcohol but had smoked 40 cigarettes/day for 40 years. He had undergone total gastrectomy, Roux-en-Y

reconstruction, and D2 lymph node dissection (Fig. 2). The histopathology of the primary lesion was poorly differentiated adenocarcinoma, $po1>sig$, MP, $INF\beta$, Ly1, V1, CY0, N1 (#3), PM-, DM- (Fig. 3). On immunohistochemistry, the tumor cells were positive for AE1/AE3, p53, and CEA, and the MIB-1 index was 20% (Fig. 4). The cancer was stage IIA, and he had not received postoperative adjuvant chemotherapy at that time. Since the results of the adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) were reported in 2006, 1-year oral TS-1 therapy for stage II, IIIA, and IIIB patients is now recommended in Japan (1, 2); however, no recommendations for adjuvant chemotherapy had been made when the patient in this report underwent gastrectomy.

No signs of recurrence were observed for a long time. However, after 12 years, he was admitted to the hospital with left jugular swelling. Computed tomography revealed supraclavicular lymph node (Virchow lymph node) swelling and precordial subcutaneous edema. Hematological and biochemical findings revealed the absence of renal or liver failure; however, the levels of carcinoembryonic antigen (CEA) were abnormally high (Table 1). The specimens from the



Figure 1. Findings of upper gastrointestinal endoscopy performed 12 years previously: gastric cancer can be observed in the lesser curvature of the lower gastric body (arrows).



Figure 2. Resected specimen of gastric cancer.

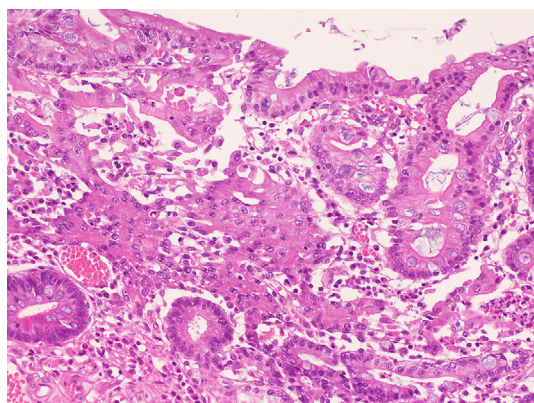


Figure 3. Histopathology of the primary lesion revealed a poorly differentiated adenocarcinoma on Hematoxylin and Eosin staining (magnification, $\times 40$).

left supraclavicular lymph node indicated late recurrence of the gastric cancer.

The patient rejected intravenous chemotherapy; therefore, we administered oral tegafur/gimeracil/oteracil combination therapy (TS-1[®]). However, after three months, the metastatic tumor in the neck increased in size rapidly, and the supraclavicular lymph node disintegrated (Fig. 5A) with pain. Radiotherapy (2 Gy over 25 days; 50 Gy in total) was administered to the left cervix, along with TS-1 and cisplatin combination therapy (3). After we administered one cycle of chemotherapy, the metastatic lesion shrank markedly (Fig. 5B), but the patient showed renal disorder. Furthermore, he complained of left precordial cutaneous pain. On an examination, his left precordial cutaneous area was found to have a firm dark-reddish surface, known as carcinoma erysipeloides (Fig. 6). 18-fluorodeoxyglucose positron emission tomography revealed a high uptake of fluorodeoxyglucose in the left precordial subcutaneous tissue and the left axillary lymph nodes. The specimens from the left precordial cutaneous tissue revealed a poorly differentiated adenocarcinoma (Fig. 7); on immunohistochemistry, the tumor

cells were positive for AE1/AE3, p53, and CEA, and the MIB-1 index was 80% (Fig. 8). These findings were similar to the immunohistochemistry findings of the primary lesion. We therefore made a diagnosis of cutaneous metastasis that originated from the gastric cancer.

Accordingly, we changed the regimen to TS-1+oxaliplatin combination therapy (4) and planned to administer radiotherapy to the left precordial cutaneous tissue. Although concurrent chemotherapy was initially effective, the patient complained of worsening general malaise and decided to discontinue chemotherapy after seven months and refused to start radiotherapy. The patient ultimately died due to deterioration of his condition at eight months after the recurrence of the gastric cancer (Fig. 9).

Discussion

We encountered a rare case of cutaneous and lymph node metastases that recurred 12 years after radical total gastrectomy for stage IIA gastric cancer. The current report describes two important points: first, gastric cancer recurred after more than 12 years, and second, cutaneous metastases arose from gastric cancer.

The treatment outcome of gastric cancer is generally evaluated using the five-year survival rate, and outpatient follow-up is usually performed up to five years after the initial surgery (5, 6). This is because only 2.8-10.8% of patients with gastric cancer experience relapse more than 5 years later, and only 0.9-2.0% of patients show relapse beyond 10 years later (3, 5, 6). On rare occasions, gastric cancer has recurred and metastasized more than 20 years after surgery according to previous reports (bone metastasis (7), and peritoneal recurrence (8)). However, there have been no reports of cutaneous metastasis that recurred more than 20 years after surgery.

Patterns of late recurrence

The patterns of recurrence of gastric cancer include distant metastasis (hematogenous or lymphatic), peritoneal me-

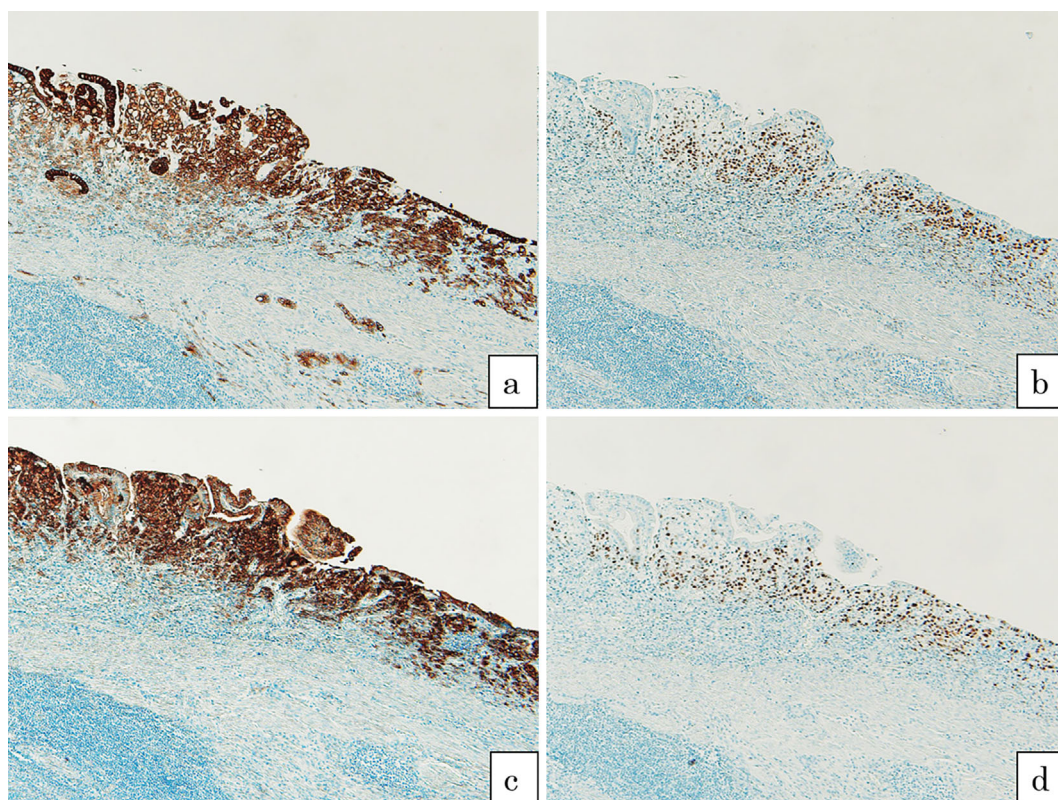


Figure 4. On immunohistochemistry, the tumor cells were positive for (a) AE1/AE3, (b) p53, and (c) carcinoembryonic antigen, and the (d) MIB-1 index was 20%.

Table 1. Laboratory Data at the Time of Admission.

WBC	4,700 /mm ³	ALP	410 mEq/L
Hb	14.6 g/dL	γGTP	15 mEq/L
Plt	30.4×10 ⁴ /μL	AMY	56 mEq/L
BUN	9.5 mg/dL	Na	140 mEq/L
Cre	0.8 mg/dL	K	4.3 mEq/L
CRP	0.1 mg/dL	Cl	103 mEq/L
TP	6 g/dL	CEA	15.2 ng/mL
Alb	3.9 g/dL	CA19-9	6.3 U/mL
T-Bil	0.8 mg/dL		
AST	11 U/L	Hight	173.5 cm
ALT	6 U/L	Weight	66.6 kg
LDH	289 U/L	BSA	1.79 m ²

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, BUN: blood urea nitrogen, Cre: serum creatinine, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Na: serum sodium, K: serum potassium, Cl: serum chloride, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen19-9, BSA: body surface area

tastasis, and locoregional metastasis. In patients with early recurrence, peritoneal metastasis is observed most frequently, followed by distant metastasis (9). In contrast, in patients with late recurrence, the most common pattern is controversial (9-11). In the current case, the histopathology of the primary lesion revealed No. 3 lymph node metastasis, and the patient showed supraclavicular and para-aorta lymph node metastasis. It was therefore suspected that the patient had experienced lymphatic metastasis.

Reasons for late recurrence

Shiraishi et al. reported that late-recurrence gastric cancer (more than 2 years after the operation) has several distinct features compared to early-recurrence gastric cancer, including a small size (<8 cm) and negative or limited lymph node metastases (especially for the perigastric lymph nodes) (12). Moon et al. reported that late recurrence of gastric cancer can be influenced by second primary cancers (13). However, there are no valuable indicators for predicting ≥10-year re-

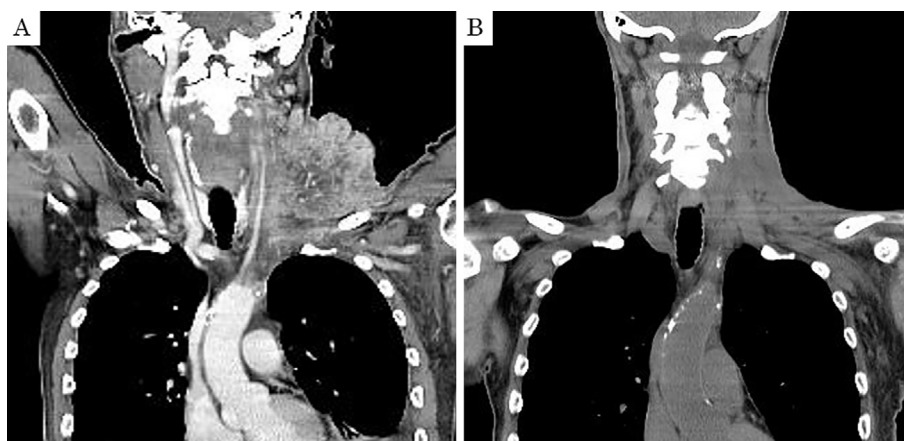


Figure 5. (A) A cervical computed tomography scan in the sagittal plane obtained before irradiation and chemotherapy revealed the increase in the size of the metastatic supraclavicular lymph node. (B) A cervical computed tomography scan in the sagittal plane obtained after irradiation and chemotherapy revealed that the metastatic lesion had shrunk markedly.



Figure 6. The left precordial cutaneous tissue showed a firm, dark-reddish surface.

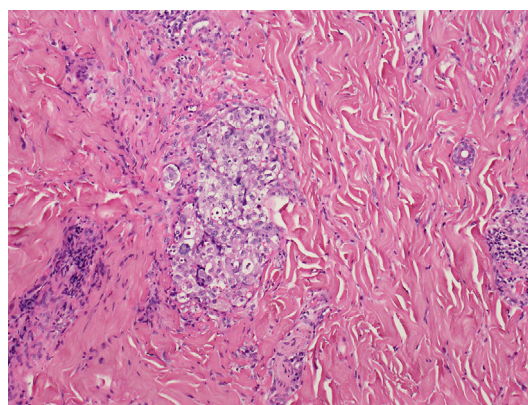


Figure 7. The resected specimen from the left precordial subcutaneous tissue revealed poorly differentiated adenocarcinoma on Hematoxylin and Eosin staining (magnification, $\times 20$).

currence of gastric cancer. Iwanaga et al. described the reasons for late recurrence as follows: (a) only a few cancer cells may have remained after surgery; (b) the remaining cancer cells might be located at a site where spread is difficult; (c) the cells may proliferate slowly; or (d) the host's immunity may be active (14). According to that study, the presence of cells after surgery may be deduced based on the depth of the carcinoma, vascular invasion and the proximal margin (PM) or distal margin (DM). The spreading difficulty of the few remaining cells may be deduced based on the location of the residual tumor, infiltrative growth (INF), and desmoplastic reaction in the serosa (s) or the serosal lower layer (ss). The slow proliferation of cells may be evaluated using the mitotic index, the survival period from the time of recurrence to the time of death, and the period from the disease diagnosis to initial surgery. The host's immunity may be evaluated based on the desmoplastic reaction in the tumor and the total lymphocyte count before surgery.

After evaluating the preoperative condition of the present

patient, we found some markers of possible late recurrence of gastric cancer: slight lymph node metastasis, a low mitotic index (Fig. 10), and total lymphocyte count $>3,000$. However, some other markers do not support the possibility of late recurrence (Table 2). Therefore, it was difficult to anticipate late recurrence in this patient. The further development of supplementary therapeutic measures is expected to reduce the incidence of late recurrence of gastric cancer.

Another report focused on the MIB-1 index (15). MIB-1 is a Ki-67-equivalent murine monoclonal antibody that reflects the degree of cell proliferation. MIB-1 is expressed in all phases of the cell cycle except for G₀. While the expression of MIB-1 only indicates that a cell is currently replicating, the MIB-1 index is considered to correlate with the degree of malignancy of gastric cancer (16). In the current case, the MIB-1 index associated with the primary lesion was 20%, which is similar to that reported in a previous study on gastric cancer (17). The MIB-1 index of the newly developed cutaneous metastasis lesion was 80%, suggesting that the metastatic lesion would have gained a high proliferative

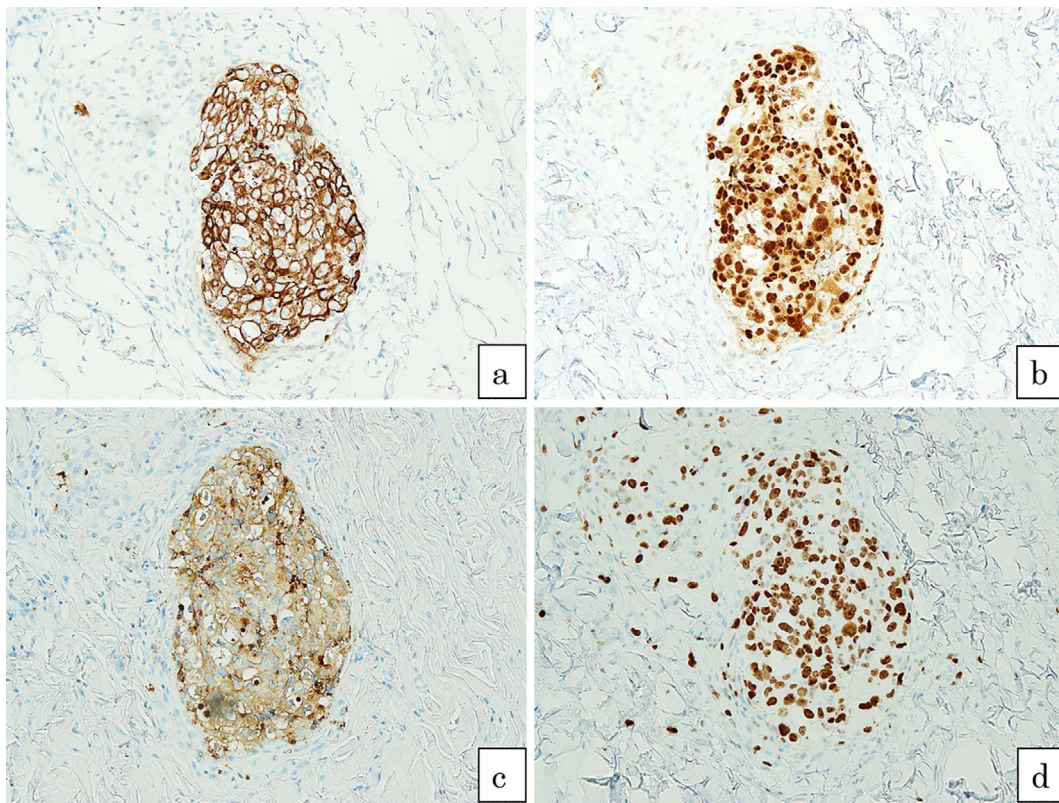


Figure 8. Immunohistochemistry of the specimen from the left precordial subcutaneous tissue revealed positivity for (a) AE1/AE3, (b) p53, and (c) carcinoembryonic antigen, and (d) the MIB-1 index was 80%.

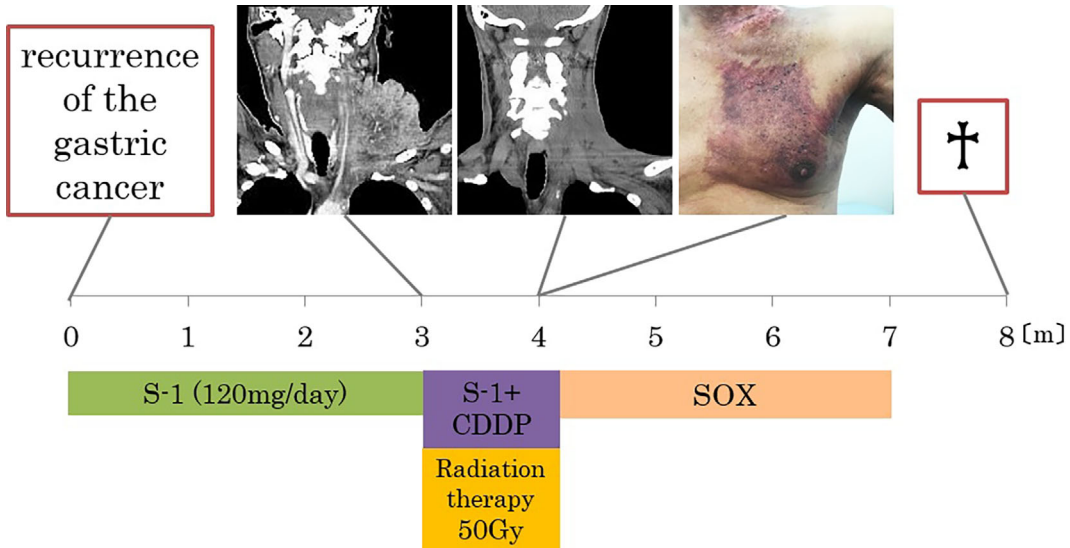


Figure 9. Clinical course of the patient from initial admission to death, along with the details of the course of chemotherapy.

eration capacity in response to certain triggering factors.

In addition to the above-mentioned criteria, the concept of “tumor dormancy” has been proposed (18). Tumor dormancy is the state in which minimal residual disease or a solitary micrometastasis is present without causing symptoms for a long duration (19, 20). However, the trigger that activates dormant cells to cause recurrence is yet to be determined. In the current case, the patient showed late recur-

rence of stage IIA gastric cancer. The histopathology of the primary lesion was p01 and N1. Accordingly, it appears that the remaining cancer cells were poorly located for spreading, which may be why recurrence occurred after 12 years of tumor dormancy.

Since the interim analysis of the ACTS-GC trial was reported in 2007 (21), one-year adjuvant chemotherapy has been recommended for stage II or III gastric cancer. How-

ever, when the current patient underwent surgery, there was no such recommendation, and he did not receive adjuvant chemotherapy. If adjuvant chemotherapy had been performed, it might have reduced the risk of cancer recurrence.

Late cutaneous metastasis

Cutaneous metastasis of gastric cancer is rare, with an incidence of only 1.7-2.0% (22, 23). Cutaneous metastasis is classified into the following three categories: (a) nodular

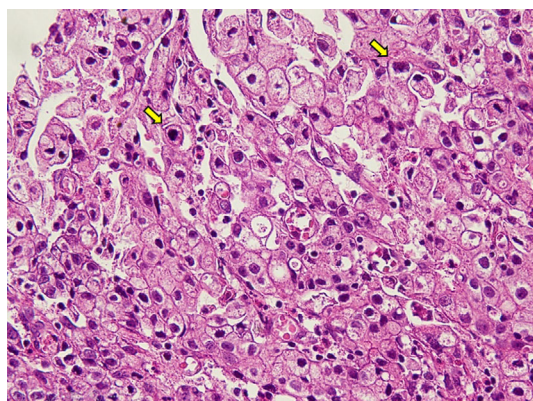


Figure 10. Histopathology of the primary lesion on Hematoxylin and Eosin staining (magnification, $\times 40$). A few mitotic cells (yellow arrow) were observed.

type, (b) inflammatory type, and (c) sclerodermoid type (24). The nodular type is relatively common, but the current case showed the inflammatory type, i.e., carcinoma erysipeloïdes. Carcinoma erysipeloïdes is similar to acute cutaneous infection, but unlike cutaneous infection, carcinoma erysipeloïdes does not result in a fever or leukocytosis, and antibiotics are ineffective (23, 25).

To our knowledge, only 2 cases of cutaneous metastasis of gastric cancer that recurred after >10 years have been reported (Table 3); we found these cases by searching the PubMed database for cases between 1980 and 2019 with the keywords “gastric carcinoma” and “delayed cutaneous metastasis” (26, 27). Including the current case, the mean age of recurrence was 66 years old, and all cases showed poorly differentiated adenocarcinoma on histopathology. One patient (27) underwent adjuvant chemotherapy with 5-fluorouracil and cisplatin combination therapy, and two patients, including our own, did not undergo adjuvant chemotherapy at all (26). The mean time from surgery to recurrence was 11 years, and the mean period from recurrence to death was 9.5 months. As the mean survival time has been estimated to be 7.5 months (28), the presence of cutaneous metastases appears to indicate a poor prognosis.

According to the ACTS-GC trial, one-year adjuvant TS-1 therapy for stage II, IIIA, and IIIB patients improved the five-year overall survival and relapse-free survival. Further-

Table 2. Reasons for Late Recurrence in the Current Case.

Were few cancer cells left at the time of surgery?	Superficial carcinoma (M or SM)	No
	Vascular invasion is slight	No
	Lymph node metastasis is slight	Yes
	The PM or DM of the residual tumor is small	-
Were the remaining few cancer cells present at a difficult-to-spread location?	The PM or DM of the residual tumor is located in mucosa	-
	The tumor invasion in the serosa shows $INF\alpha$ or $INF\beta$	-
	Desmoplastic reaction in s or ss is positive	-
Was cancer proliferation slow?	Low mitotic index	Yes
	Long time from recurrence	No
	Long time from initial surgery	No
Was the host's resistance active?	Desmoplastic reaction in the tumor is positive	No
	Total lymphocyte count before surgery $>3,000/\mu\text{L}$	Yes

PM: proximal margin, DM: distal margin, INF: infiltrative growth

Table 3. Cases of Cutaneous Metastasis of Gastric Cancer That Recurred after >10 Years.

Age	Sex	Histopathology	Stage of primary cancer	Adjuvant Chemotherapy	The type of ctaneous metastasis	Terms from gastrectomy to relapse	Terms from relapse to death	Reference
72	M	poorly differentiated adenocarcinoma	stage IIA	none	inflammatory type	10 years	2.5 months	26
64	F	poorly differentiated adenocarcinoma	stage IIIB	5FU+CDDP	inflammatory type	11 years	22 months	27
62	M	poorly differentiated adenocarcinoma	stage IIA	none	inflammatory type	12 years	4 months	our case

more, the relapse rate of lymph node and peritoneal metastasis was significantly reduced (2). There are no data regarding the efficacy of adjuvant chemotherapy for more than 10 years; however, it is possible that our patient might not develop late lymph node recurrence, as shown by the 5-year data.

Conclusion

We reported a rare case of cutaneous and lymph node metastases that recurred 12 years after radical total gastrectomy for stage IIA gastric cancer. Careful observation is necessary despite the rarity of recurrence after more than five years.

Informed consent was obtained from the patient for inclusion in this study and publication of this case.

The authors state that they have no Conflict of Interest (COI).

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