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CASE REPORT

Late recurrence of gastric cancer in the ovary and uterine cervix

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Abstract Uterine cervical metastasis from gastric cancer is relatively rare. This is a report of an extremely rare instance of concurrent late gastric-cancer recurrence to the left ovary and the uterine cervix, 11 years after initial treatment. A 53-year-old woman was referred to our hospital with continuous abdominal pain and genital bleeding. Eleven years prior, she had been treated for gastric cancer, pathologically confirmed as stage II poorly differentiated adenocarcinoma with signet-ring cell carcinoma (pT2N1M0). Magnetic resonance imaging results showed a solid mass in the left ovary, about 8 cm in diameter, fixed to the enlarged uterus and displaying slightly high intensity on T1-weighted images and uneven low intensity and enhanced hypervascular areas on T2-weighted images. Cervical biopsy revealed small, round, spindle-shaped tumor cells beneath a normal cervical epithelium. When we did the immunohistochemistry tests, the tumor cells were positive for cytokeratin 5.2, cytokeratin anion exchange protein 1/3, and cytokeratin 7; the cells were negative for cytokeratin 20 and paired-box gene (PAX) 8. This marker pattern was the same as that of her previous gastric cancer; therefore, the tumors of the cervix and left ovary were diagnosed as metastatic gastric cancer. After obtaining informed consent, the patient received transarterial chemoembolization using cisplatin and, subsequently, underwent a modified radical hysterectomy, bilateral salpingo-oophorectomy. Pathological examination revealed an infiltrative pattern with poorly differentiated adenocarcinoma and signet-ring cell carcinoma. The patient received combination chemotherapy with cisplatin and S-1, and she is currently alive 12 months after surgery with no evidence of recurrence. Late recurrence more than 10 years after treatment for primary gastric cancer is extremely rare. Clinicians should be aware of the possibility of metastasis from extrapelvic carcinomas, even in patients treated many years prior to presentation.

Keywords Gastric cancer · Late recurrence · Ovarian metastasis · Uterine cervical metastasis

Introduction

Ovarian metastasis from gastric cancer, the so-called Krukenberg tumor, is sometimes seen, but uterine cervical metastasis is relatively rare. The uterine cervix is an infrequent site of metastasis, in general; the postulated reasons include its small size, low blood flow, distal circulation status, and its abundant content of fibrous tissue [1, 2].

Lemoine et al. reported that the most common extragenital neoplasms to metastasize to the cervix derive from the stomach (28.7 %), the ovary (26.4 %), the large bowel (24.1 %), and the breast (16.1 %), with all other sites accounting for 4.6 % [2]. Based on this report and other literature reviews, the majority of primary tumors are gastric, breast, colorectal, and ovarian. It is relatively rare to see gastric cancer metastasizing to the cervix more than 5 years after surgery for the primary cancer [3].

This is a report of an extremely rare instance of late gastric-cancer recurrence to the left ovary and uterine cervix, 11 years after the initial treatment. We describe the

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radiological, morphological, and clinical features, and we also perform a literature review.

Case report

A 53-year-old gravida 0 para 0 Japanese woman was referred to our hospital with abdominal pain and genital bleeding. Her referring physician noted a suspicious left ovarian tumor. Eleven years prior, she underwent distal gastrectomy with Roux-en-Y reconstruction for gastric cancer. The tumor was pathologically confirmed as stage II poorly differentiated adenocarcinoma (pT2N1M0). Her familial history was unremarkable. On pelvic examination, the uterus was enlarged, about 120 × 80 mm in diameter and fixed to the swollen left adnexa. Palpation revealed the organ to be hard, uneven, and tightly adherent to the surrounding structures, such as rectum, bladder, and retroperitoneum. Diffuse induration was detected in the uterine cervix and the upper part of the vaginal wall.

Magnetic resonance imaging results showed a solid tumor in the left ovary, about 8 cm in diameter, fixed to the enlarged uterus. The mass had slightly high intensity on T1-weighted images and a patchy pattern, uneven low intensity, and enhanced hypervascular areas on T2-weighted images. The uterine cervix and the left side of the uterine corpus demonstrated isointensity on T1-weighted images and low intensity on T2-weighted images, with poor enhancement (Fig. 1). Positron-emission tomography and computed tomography demonstrated areas of abnormal 18F-fluorodeoxyglucose uptake in the uterine cervix and the left ovarian tumor; however, the extent of uptake was not particularly high (maximum standardized uptake value: early 3.5, delayed 3.8). The differential diagnosis included a metastatic gastric cancer to the uterus and left ovary, a malignant Brenner tumor of the left ovary, and a malignant mesenchymal tumor of the uterus. Cervical cytology was positive for adenocarcinoma, and endometrial cytology was negative. Colposcopy revealed that the portio vaginalis and the vaginal wall were slightly deformed, having an ischemic epithelium and an irregular and rough surface.

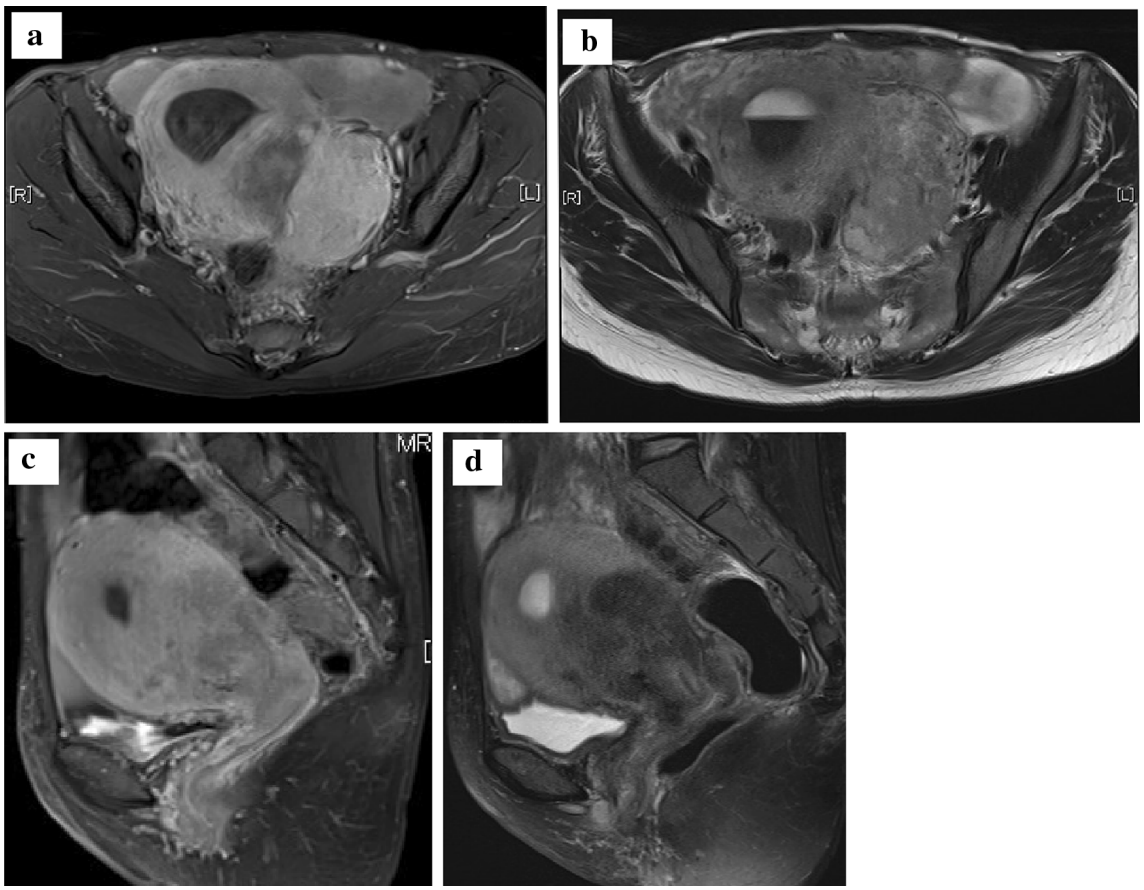

Fig. 1 Pelvic MRI findings. MRI showed a solid tumor in the left ovary, about 8 cm in diameter. The mass had slightly high intensity on T1-weighted images and a patchy pattern, uneven low intensity, and enhanced hypervascular areas on T2-weighted images. The uterine cervix and the *left* side of the uterine corpus demonstrated isointensity on T1-weighted images and low intensity on T2-weighted images, with poor enhancement. **a**, **c** T1-weighted and Gadlinium enhanced image. **b**, **c** T2-weighted images

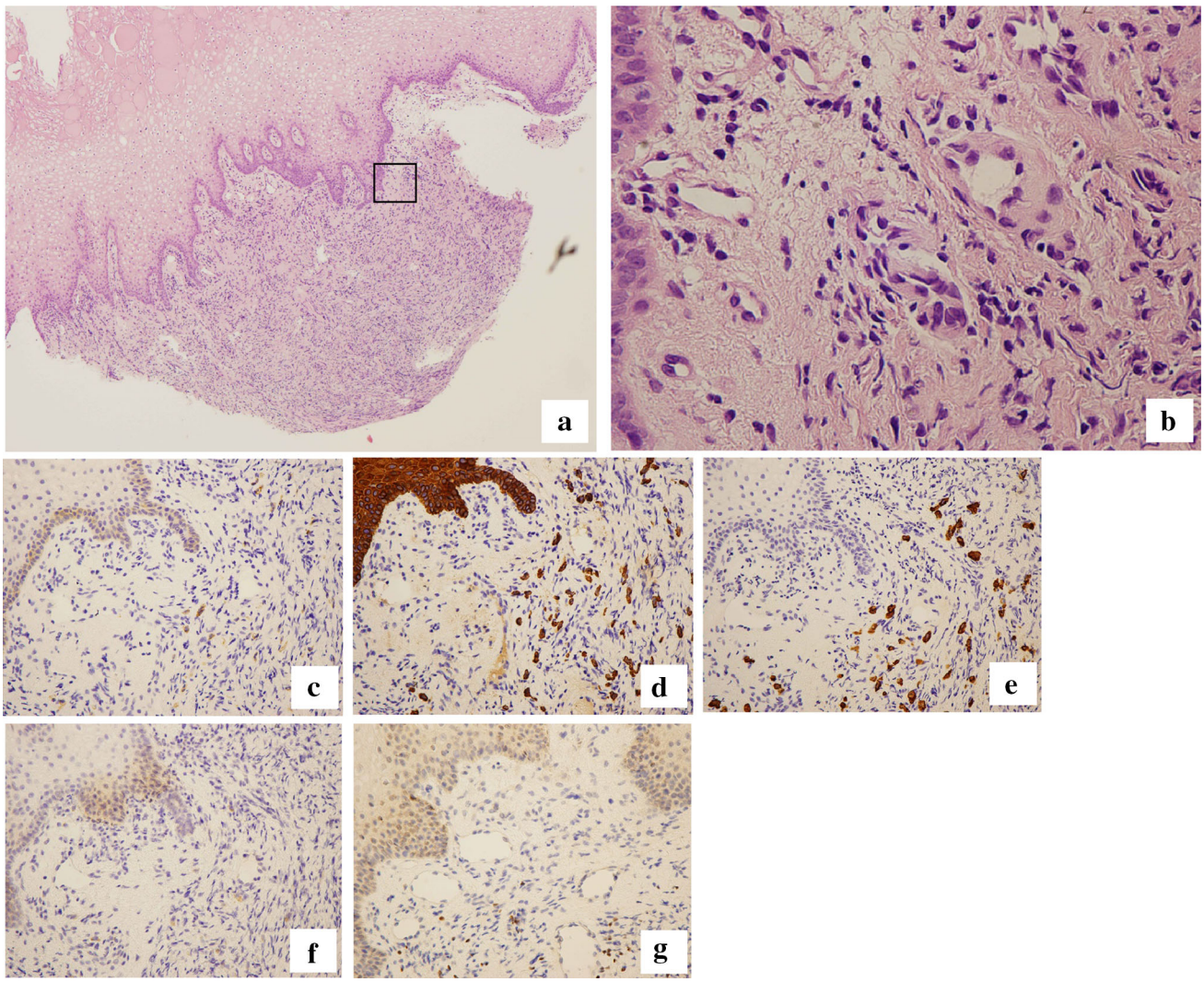

Fig. 2 Pathological examination (cervical biopsy). Cervical biopsy showed small, round, spindle-shaped tumor cells with atypia along with inflammatory-cell infiltration and fibrosis beneath a normal cervical squamous epithelium (**a**, **b**). Panel **b** is an enlarged view of the square of the part in **a**. On immunohistochemistry, the tumor cells were diffusely positive for CAM 5.2 (**c**), AE1/AE3 (**d**), and CK 7 (**e**). The cells were negative for CK 20 (**f**) and PAX8 (**g**). (**a** H&E, original magnification ×4, **b** H&E ×40, **c**–**g** ×20)

Cervical biopsy showed small, round, spindle-shaped tumor cells with atypia along with inflammatory-cell infiltration and fibrosis beneath a normal cervical squamous epithelium (Fig. 2a, b). When we did the immunohistochemistry tests, the tumor cells were diffusely positive for cytokeratin (CAM) 5.2, cytokeratin anion exchange protein (AE) 1, AE3, and cytokeratin (CK) 7. The cells were negative for CK 20 and paired-box gene (PAX) 8 (Fig. 2c–g). Upon review of the patient's gastric cancer treated 11 years prior, the pathological findings showed mostly poorly differentiated adenocarcinoma with some areas of signet-ring cell carcinoma (Fig. 3a, b). On immunohistochemistry, the staining pattern of these tumor cells was the same as that obtained from the current cervical sample (Fig. 3c–g). Therefore, the tumor of the cervix and the left ovary was diagnosed as a metastatic tumor from the patient's previous gastric cancer. No abnormalities were observed on gastrofiberoscopy.

Laboratory studies showed an elevated lactate dehydrogenase level of 1088 IU/mL (normal 119–229 IU/mL), a C-reactive protein level of 10.6 mg/mL (normal <0.3 mg/mL), and a D-dimer level of 8.4 μg/mL (normal <1.0 μg/mL). The patient's carcinoma antigen (CA) 125 level was elevated at 82 U/mL (normal <35 U/mL), but CA19–9 and carcinoembryonic antigen (CEA) levels were within normal limits.

As these studies were underway, the patient's abdominal pain was getting worse and her genital bleeding was continuing; she was taking oral oxycodone, up to 260 mg per day, for pain relief. After obtaining informed consent, the patient received transarterial chemoembolization (TACE) of both uterine arteries with the goal of tumor regression,

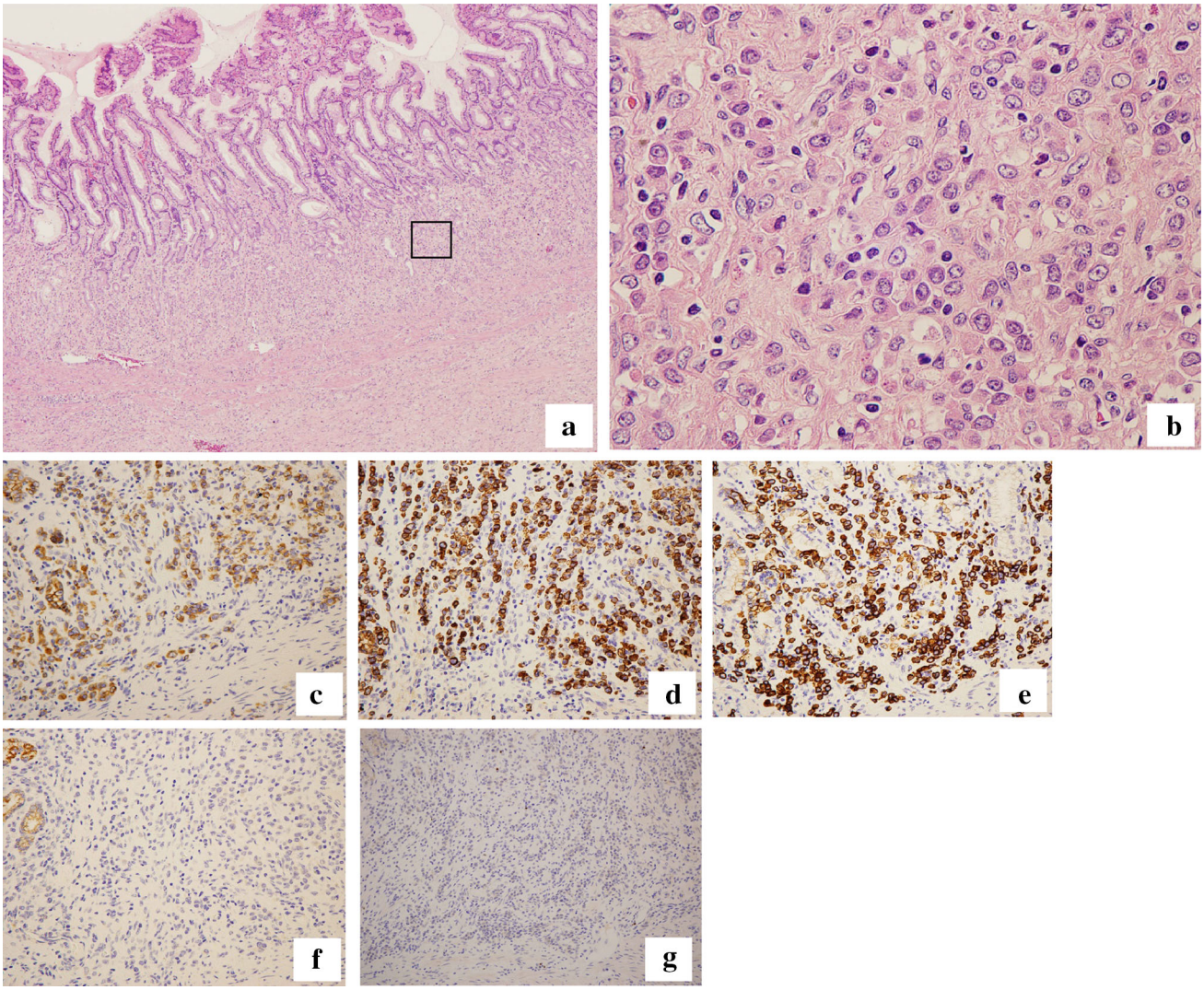

Fig. 3 Pathological examination (gastric cancer). The pathological findings showed mostly poorly differentiated adenocarcinoma with some areas of signet-ring cell carcinoma (**a**, **b**). Panel **b** is an enlarged view of the *square* of the part in **a**. On immunohistochemistry, the tumor cells were diffusely positive for CAM 5.2 (**c**), AE1/AE3 (**d**), and CK 7 (**e**). The cells were negative for CK 20 (**f**) and PAX8 (**g**). (**a** H&E, original magnification ×4, **b** H&E ×40, **c**–**g** ×20)

pain reduction, and control of genital bleeding. The TACE regimen consisted of cisplatin for chemotherapy and Gelfoam (Pfizer Inc., NY, US) for embolization. The size of the cervical and left ovarian tumors decreased after treatment, and the patient's numeric rating-scale [4] value for abdominal pain decreased from 10 to 5. Her genital bleeding also decreased after treatment. After obtaining informed consent, we performed a laparotomy, both to relieve her continuous abdominal pain by tumor debulking and to obtain a definitive pathological diagnosis.

Intraoperative inspection revealed a small amount of ascites, an enlarged uterus fixed to a left ovarian tumor, and a right ovary that appeared slightly enlarged due to an apparent endometrial cyst. The tumor spread from the retroperitoneum of the cul-de-sac to the deep part of both uterosacral ligaments (Fig. 4). We performed a modified radical hysterectomy (Piver type II) [5], bilateral adnexectomy, with hypogastric nerve (pelvic plexus) amputation for pain relief.

The left ovarian tumor was predominantly solid, and hard, and the cut surface revealed grayish yellow, relatively homogenous tissue with a small amount of hemorrhage and necrosis. A small amount of residual tumor was unfortunately present on the rectum (Fig. 4); this was not resected, because of the possibility of microscopic malignant cells around the tumor, making eventual recurrence very likely if a low anterior resection was performed. In addition, the patient's disease had a poor prognosis, and we wanted to avoid colostomy to maintain her quality-of-life. After surgery, her numerical pain rating-scale value decreased

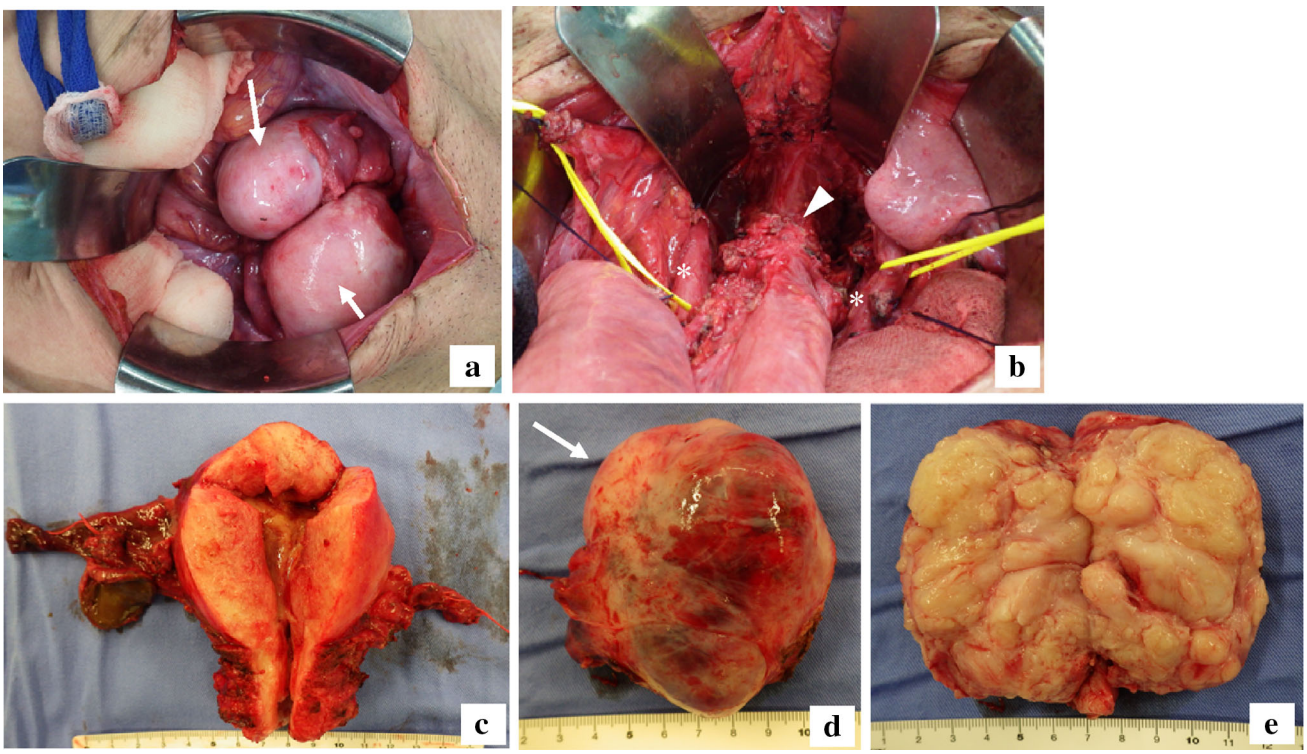

Fig. 4 Macroscopic findings. Intraoperative inspection revealed an enlarged uterus (*arrow*) fixed to a left ovarian tumor (*long arrow*) (**a**–**c**). The tumor spread from the retroperitoneum of the cul-de-sac to the deep part of both uterosacral ligaments. The left ovarian tumor was predominantly solid and hard, and the cut surface revealed *grayish yellow*, relatively homogenous tissue with a small amount of hemorrhage and necrosis (**d**–**e**). A small amount of residual tumor was unfortunately present on the rectum (*arrowhead*). (*Asterisk* indicates ureter.)

from 10 to 0, although she did experience transient urinary-bladder dysfunction.

Pathological examination revealed an unencapsulated, infiltrative pattern with poorly differentiated adenocarcinoma, predominantly consisting of signet-ring cell carcinoma in the left ovarian tumor. The cervical tumor also demonstrated an infiltrative pattern with poorly differentiated adenocarcinoma and some areas of signet-ring cell carcinoma beneath normal cervical squamous and glandular epithelium. On immunohistochemistry, the tumor cells in the ovary and the uterine cervix were diffusely positive for AE1/AE3, and negative for PAX8 (Figs. 5, 6). Mitotic figures in these tumor cells were identified, with a mitotic count of over 10 per 10 high-power fields. The final diagnosis was metastatic carcinoma from the patient's previous gastric cancer. The right ovary was pathologically proven to be an endometrial cyst without metastasis.

After surgery, the patient received 6 cycles of combination chemotherapy using cisplatin and S-1 (tegafulgimeracil,-oteracil potassium; TAIHO Pharmaceutical Co., Ltd., Japan), because she was at high risk for re-recurrence given the residual disease on the rectum. She is currently alive 12 months after surgery, with no evidence of recurrence.

Discussion

Several authors have reviewed patients with metastatic cervical cancers; these case series had some overlap between reports [1, 2, 6]. Pérez-Montiel et al. reviewed the clinical characteristics of primary neoplasms metastasizing to the uterine cervix; they included 45 patients with gastric cancer, 36 patients with breast cancer, 36 patients with ovarian cancer, and 19 patients with colorectal cancer [1]. They reported that the median age is lower in patients with gastric cancer than for those with other malignancies: 43, 54.5, 53, and 59 years for gastric, breast, ovarian, and colorectal cancer, respectively. The reported main symptoms are genital bleeding (38.7 %) and an abdominal mass (40.5 %), followed by abdominal pain (24.3 %) and abdominal distention (13.5 %). The rate of isolated metastasis to the uterine cervix in gastric, breast, ovarian, and colorectal cancer is 2.2 % (1/45), 19.4 % (7/36), 54.3 % (19/36), and 57.9 % (11/19), respectively; the incidence is, therefore, extremely rare in gastric cancer [1].

To the best of our knowledge, only 2 patients with isolated metastasis of gastric cancer to the uterine cervix have been previously reported based on postsurgical pathological findings [6, 7]. Shiraishi et al. reported that the

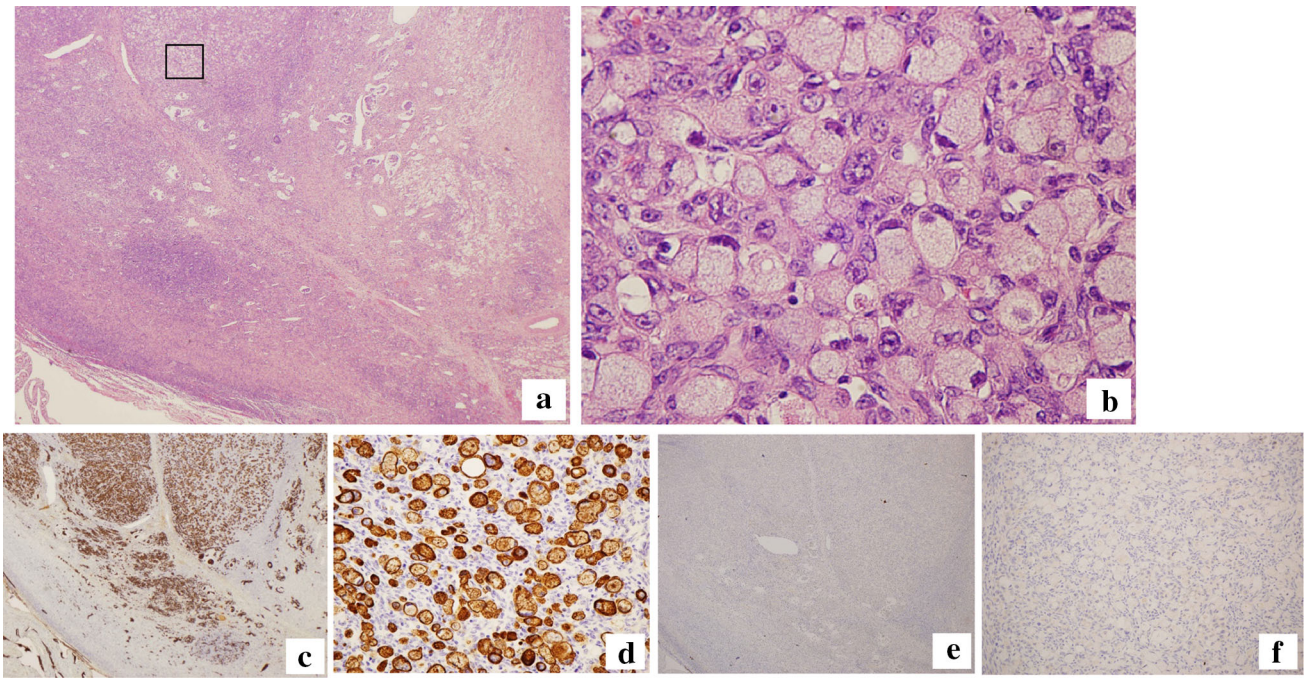

Fig. 5 Pathological examination (the left ovarian tumor). Pathological examination revealed an unencapsulated, infiltrative pattern with poorly differentiated adenocarcinoma, predominantly consisting of signet-ring cell carcinoma in the left ovarian tumor (**a**, **b**). Panel **b** is an enlarged view of the square of the part in **a**. On immunohistochemistry, the tumor cells were diffusely positive for AE1/AE3 (**c**, **d**) and negative for PAX8 (**e**, **f**). (**a** H&E, original magnification ×2, **b** H&E ×40, **c** and **e** ×2, **d** and **f** ×20)

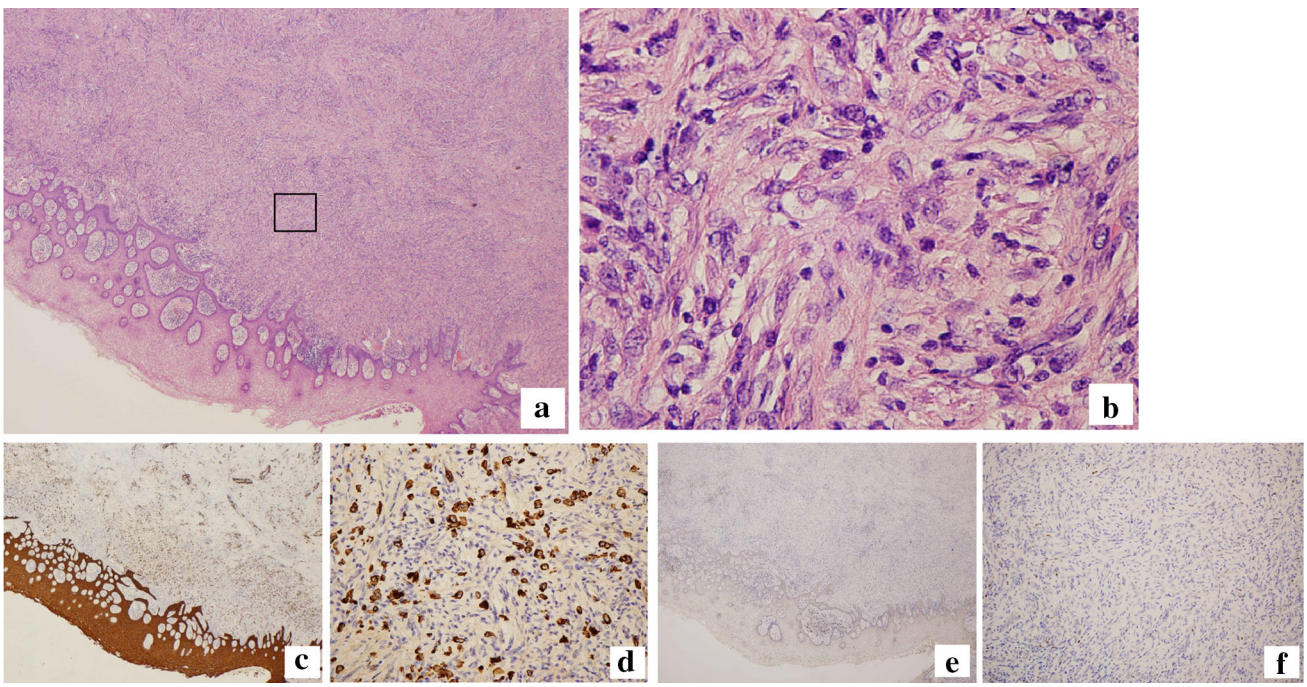

Fig. 6 Pathological examination (the cervical tumor). The cervical tumor also demonstrated an infiltrative pattern with poorly differentiated adenocarcinoma and some areas of signet-ring cell carcinoma (**a**, **b**). Panel **b** is an enlarged view of the *square* of the part in **a**. On immunohistochemistry, the tumor cells were diffusely positive for AE1/AE3 (**c**, **d**) and negative for PAX8 (**e**, **f**). (**a** H&E, original magnification ×2, **b** H&E ×40, **c** and **e** ×2, **d** and **f** ×20)

recurrence rates of gastric cancer within 2 years after surgery, more than 5 years, and more than 7 years are 75.4, 5.7, and 2.1 %, respectively [3]. In their series, cervical metastasis was diagnosed 2 years after surgery in 8 of 16 patients (50 %), and 5 years after surgery in 5 of 16 patients (31.3 %) [3]. Therefore, late metastasis to the uterine cervix from gastric cancer may not be as rare as previously thought. The authors also speculate that metastasis to the uterine cervix occurs by retrograde lymphatic dissemination and that this extension is often slow [3]. Yamamoto et al. evaluated 22 patients with recurrent disease and found that the median interval between the diagnosis of gastric cancer and the diagnosis of cervical metastasis is 22 months (range 1–121 months) [6]. However, recurrence 10 years after the diagnosis of primary gastric cancer is extremely rare, and to the best of our knowledge, only 2 patients, including our current patient, have been reported [7].

The histological type of gastric cancer in Pérez-Montiel's series was signet-ring cell in 20 patients and poorly differentiated carcinoma in 13 patients [1]. Our patient's gastric cancer was also mostly poorly differentiated adenocarcinoma with some areas of signet-ring cell carcinoma. Yamamoto reported that the initial stage of gastric cancer was stage I in 1 patient, stage IV in 18 patients, and not reported in 20 patients [6]. The later metastasis of the early stage gastric cancers, as was likely in our patient with stage II disease, to the uterine cervix is relatively rare.

Reportedly, the median survival after the diagnosis of cervical metastasis for gastric, breast, ovarian, and colorectal cancer is 5 months (range 0–20 months), 12 months (range 1.5–144 months), 4 months (range 1–21 months), and 7.5 months (range 1–48 months), respectively; the shorter survival rate is observed in gastric cancer as well as ovarian cancer [1]. The prognosis of these patients is poor, and surgery, including extirpation of the uterus, does not apparently influence the outcome. Pérez-Montiel et al. described in their review that surgery, with or without adjuvant chemotherapy or radiotherapy, was performed in 17 of 34 patients with metastatic cervical cancer from gastric cancer, while 9 of these 34 patients were treated with palliative care. However, the authors do not mention the role of surgery for these metastatic cervical cancers.

Surgery is sometimes necessary to distinguish metastatic cervical cancer from a primary cervical tumor [6]. A precise pathological diagnosis, including immunohistochemical analysis of biopsy or surgical specimens, might sometimes be essential for the accurate diagnosis of metastatic cervical carcinomas. In the current patient, immunohistochemical analysis using antibodies for CAM 5.2, AE1/3, CK 7, CK 20, and PXA8 was useful for discrimination between metastatic cervical carcinoma and primary cervical adenocarcinoma. Especially, PAX8 is a member of paired-box family of genes that have been shown to be useful to confirm primary and metastatic tumors that arise in Müllerian tract [8]. The immunoreactivity of PAX8 has been reported to be negative in gastric cancers, and positive in the majority (more than 80 %) of cervical adenocarcinomas and ovarian carcinomas [8, 9]. In the current patient, PAX8 nuclear expression was all negative in cervical and ovarian tumors as well as in the previous gastric cancer.

Moreover, our patient complained of continuous cancer-related abdominal pain, prompting the decision for palliative surgery to achieve pain relief and improved quality-of-life. Our patient experienced complete pain relief after surgery.

There is often a dilemma in decision-making, regarding the most appropriate therapeutic strategy; it is important to understand the poor prognosis and the progressive complaints involved with this condition. Our patient received combination chemotherapy with cisplatin and S-1, which is one of the regimens used in advanced or recurrent gastric cancer [10]. This regimen was apparently effective, because she is currently alive 12 months after treatment, with no evidence of recurrence. However, careful follow-up is indicated to detect any re-recurrence of her gastric cancer.

Conclusions

Late recurrence more than 10 years after the treatment of primary gastric cancer is extremely rare. Therefore, it may be difficult to obtain an accurate diagnosis in a timely fashion after symptom onset; it is also challenging to craft a definitive treatment strategy, because of the poor prognosis associated with this condition. Clinicians should be aware of the possibility of metastasis from extrapelvic carcinomas, even in patients treated many years prior to the presentation of symptoms.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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