

Successful treatment with CPT-11 plus S-1 therapy in a patient with primary signet-ring cell carcinoma of the uterine cervix: A case report and literature review

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Summary

We report our experience with a case in which primary signet-ring cell carcinoma of the uterine cervix was successfully treated with CPT-11 plus S-1 therapy. The patient was a 45-year-old woman with stage IIIB primary signet-ring cell carcinoma of the uterine cervix. The uterine cervix had enlarged to 8 cm; the right ovarian tumor was 15 cm in size; and there was an 8-cm cystic mass in the left ovary. After five cycles of CPT-11 plus S-1 therapy, the tumor shrinkage rate was 52.2% and the tumor response was partial response. To improve symptoms, left adnexectomy was performed, and CPT-11 plus S-1 therapy was continued. To date, 11 cycles have been performed without dose reduction or delay of therapy. No adverse event of grade 3 or higher has been observed. CPT-11 plus S-1 therapy was effectively and safely performed to treat signet-ring cell carcinoma of the uterine cervix that is difficult to treat. This is the first case in which primary signet-ring cell carcinoma of the uterus responded well to CPT-11 plus S-1 therapy.

Key words: Cervical cancer; Signet-ring cell carcinoma; CPT-11; S-1.

Introduction

Adenocarcinoma of the uterine cervix accounts for 10%–15% of all cases with uterine cervical cancer, and its incidence has increased in recent years. Endocervical adenocarcinoma is the most common histologic type. In contrast, signet-ring cell carcinoma (an intestinal type), which is subtype of mucinous adenocarcinoma of the uterine cervix, is very rare [1-3]. Signet-ring cell carcinoma is often metastatic. Therefore, when detected in the uterine cervix, it should be differentiated from the metastasis of gastric, breast, or other cancers. Herein, we report a case in which primary signet-ring cell carcinoma of the uterine cervix responded well to CPT-11 plus S-1 therapy, along with a review of relevant literature.

Case Presentation

A 45-year-old, gravida-2, para-0 woman presented with the chief complaint of irregular vaginal bleeding. Her past history was unremarkable. Her father had died of colorectal cancer. She had previously visited a doctor with the primary complaint of irregular vaginal bleeding that persisted for 2 months. Magnetic resonance imaging (MRI) detected a 6-cm degenerated myoma-like mass in the uterine cervix and an approximately 8-cm cystic mass in the right ovary. These masses were diagnosed as benign, and the patient was followed up. Cervical cytology was negative for intraepithelial lesion or malignancy. Levels of tumor mark-

ers were as follows: carcinoembryonic antigen, 1.6 ng/mL; cancer antigen (CA) 19-9, 7.6 U/mL; CA125, 104.1 U/mL; and squamous cell carcinoma antigen, 0.9 ng/mL. Irregular vaginal bleeding persisted. Four months after the first visit, MRI revealed enlargement of the mass from 6 to 8 cm for the uterine cervix and from 8 to 10 cm for the right ovarian tumor, as well as a new 7-cm cystic mass in the left ovary. Computed tomography (CT) revealed hydronephrotic kidney on the left as well as masses in the greater omentum and peritoneum, suggesting dissemination in addition to the presence of ascites. No abnormal findings were evident on upper or lower gastrointestinal endoscopy. As ovarian cancer was suspected, the patient was referred to our hospital. Degenerative tissue was obtained via cervical histology performed on the patient's first visit to our hospital, for which malignancy could not be ruled out. Internal examination revealed a barely movable lower abdominal mass reaching to three fingerbreadths above the umbilicus. The uterine cervix was difficult to observe because the vaginal wall was stiff and poorly expandable. Because ovarian cancer and peritonitis carcinomatosa were suspected, probe laparotomy was performed for biopsy of peritoneal dissemination, which led to the diagnosis of signet-ring cell carcinoma (Figure 1). The second cervical histology also detected signet-ring cell carcinoma. Moreover, adenocarcinoma *in situ* was detected in the lesion (Figure 2). Immunostaining results of the cervical tissue were as follows: CK7 (+), CK20 (+), PAX8 (-), ER (-), PgR (-), GCDFFP-15 (-), mammaglobin (-), CDX-2 (+), and p16 (+) (Figure 3).

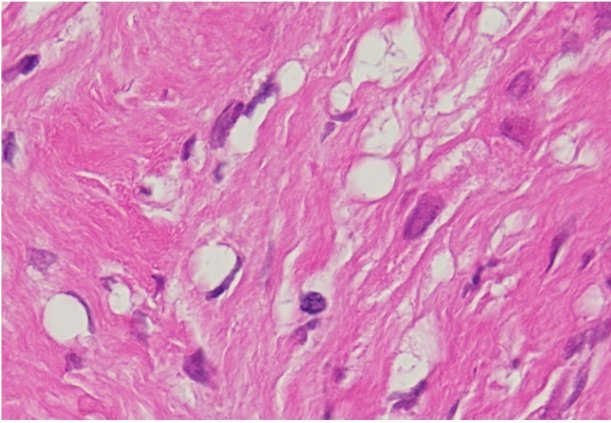


Figure 1. — Peritoneal biopsy (H&E staining). Invading signet-ring cell-like atypical cells with funicular and alveolar configurations and background fibrous tissue. Tumor was diagnosed as adenocarcinoma, specifically metastasized signet-ring cell carcinoma.

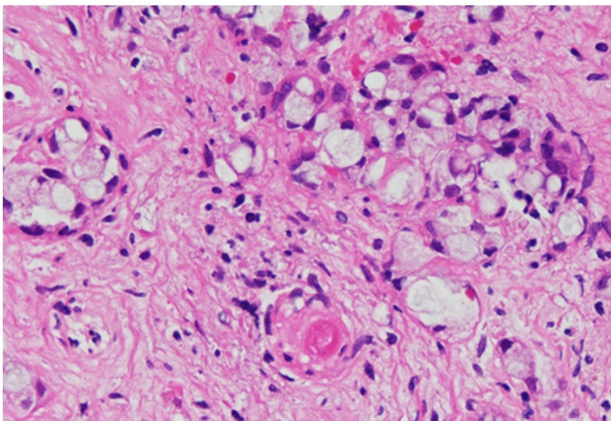


Figure 2. — Histological findings in the cervix (H&E staining). Invading and proliferating mucin-producing atypical cells with minute funicular, alveolar, and tubular structures and showing high fibrosis levels. These histological findings are almost similar to those found by peritoneal biopsy and are consistent with adenocarcinoma. Signet-ring cell-like atypical cells are noted.

Gastric cancer metastasis was suspected, and upper gastrointestinal endoscopy and gastric biopsy were performed in our hospital. However, there was no evidence of malignancy. Moreover, postoperative contrast-enhanced CT revealed no findings suggestive of primary lesions in other organs. Based on these findings, the patient was diagnosed with stage IIIB signet-ring cell carcinoma of the uterine cervix (pT3b, NX, and M0). Five cycles of CPT-11 plus S-1 therapy (CPT-11 50 mg/m² on day 1; S-1 120 mg/body on days 1–21, q 35 days) were performed as postoperative chemotherapy. The right ovary shrunk from 15.2 to 6.6 cm and the left ovary from 8.2 to 4.6 cm (Figure 4). The tumor reduction rate was 52.2%, and tumor response evaluation, based on RECIST, indicated partial response (PR). Al-

though ovarian tumors had been minimized, the patient continued abdominal bloating. Therefore, left adnexectomy was performed to reduce tumor volume. Signet-ring cell carcinoma was also detected in the left ovary (Figure 5). To date, 11 cycles of CPT-11 plus S-1 combination therapy have been performed continuously.

Observed adverse events were only grade 1 nausea and malaise. Regarding hematological toxicity, there was no grade 3 or higher leucopenia, neutropenia, anemia, or thrombocytopenia. Thus, reducing of drug dose or delay of therapy was not needed. Fourteen months have passed since the initial treatment, and the patient continues receiving chemotherapy without disease progression.

Discussion

Among adenocarcinomas of the uterine cervix, the endocervical type is believed to be the most common [4]. Signet-ring cell carcinoma—an intestinal type and subtype of mucinous adenocarcinoma of the uterine cervix—is rare. Therefore, when it is detected in gynecological organs, it is necessary to differentiate it from the metastases of gastric, breast, and other cancers.

There is no established therapy for cervical signet-ring cell carcinoma. Herein, we report this rare case and review from the literature.

In the present case, since no primary lesion was detected in organs other than the uterine cervix and adenocarcinoma in situ was detected in the uterine cervical lesion, the patient was diagnosed with primary signet-ring cell carcinoma of the uterine cervix.

Our PubMed search yielded 15 cases of signet-ring cell carcinoma of the uterine cervix, as summarized in Table 1 [1-3, 5-14]. Among these patients, six stage IB patients, two stage IIB patients, two stage III patients, and one stage IV patient were treated surgically. Moreover, regarding adjuvant therapy, three stage IB patients and one stage III patient received radiotherapy; two stage IB patients, one stage III patient, and one stage IV patient received chemotherapy; and one stage IB patient received concurrent chemoradiotherapy (CCRT). Furthermore, two stage III patients received CCRT and two stage IV patients received systemic chemotherapy as initial therapies. In reports on chemotherapy, cisplatin plus etoposide [1], paclitaxel plus carboplatin [7], and paclitaxel plus cisplatin plus bevacizumab [14] therapies were used. The number of cases is small, and there is no high-evidence level therapy for primary signet-ring cell carcinoma of the uterine cervix. Thus, we presume that different treatment regimens were used according to individual patients.

The effectiveness of CPT-11 plus S-1 therapy has been proved as a first-line chemotherapy approach for patients with unresectable advanced or recurrent gastric cancer. Narahara *et al.* reported that among 94 patients with advanced or recurrent gastric cancer, the response rate was 41.4%, the median time to treatment failure was 4.5 months, and the median overall survival time was 12.8 months [15].

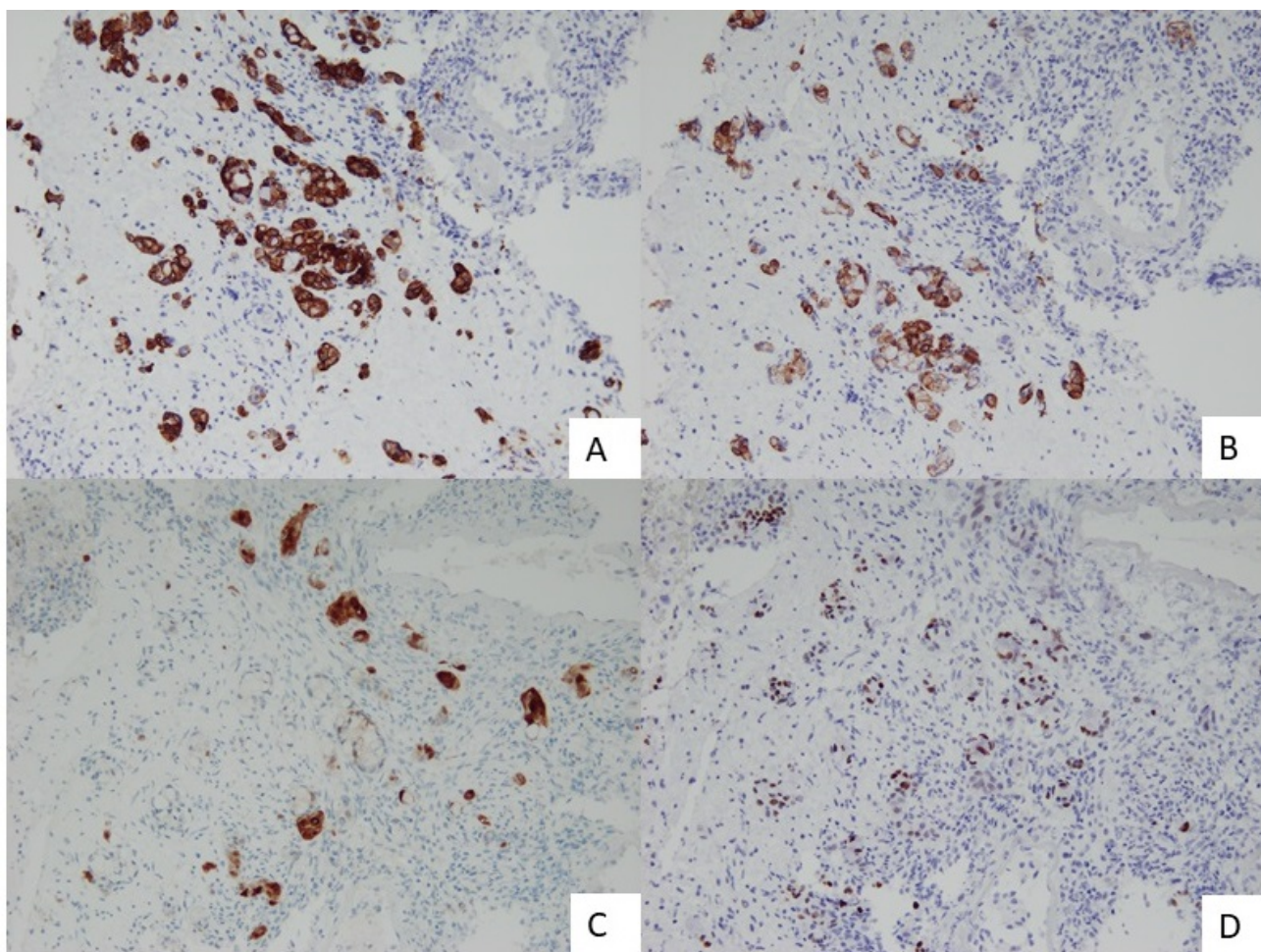


Figure 3. — Histological findings in the cervix (immunostaining). Positivity for CK7, CK20, p16, and CDX-2 and negativity for PAX8, ER, PgR, GCDFP-15, or mammaglobin are noted.

Since our case presented with an ovarian tumor that reached to three fingerbreadths above the umbilicus, in addition to peritoneal dissemination, CCRT was not suitable. Instead, postoperative systemic chemotherapy was selected. The standard regimen for cervical cancer is TP (paclitaxel + cisplatin) therapy. However, considering that the histologic type was signet-ring cell carcinoma, CPT-11 plus S-1 therapy was administered after obtaining the patient's consent.

After five cycles of therapy, PR was observed, indicating that the treatment was effective. In a typical situation, chemotherapy would have been continued. However, since the tumors continued making the patient feel bloated, left adnexectomy was performed once the 5 cycles were completed. Following left adnexectomy, the CPT-11 plus S-1 combination therapy was continued as postoperative chemotherapy. As of now, 11 cycles have been performed. There has been no disease progression, and no serious adverse events have occurred. Therefore, we believe CPT-11 plus S-1 therapy to be effective against primary signet-ring cell carcinoma of the uterine cervix. In general, the prognosis of signet-ring cell carcinoma is believed to be poor. Among the 15 reported patients with primary signet-ring cell carcinoma of the uterine cervix, stage IIIB patients ei-

ther died within 18 months or experienced relapse after 6 months. Patients with good prognoses only exhibited early-stage cancer and in many, the lesions were completely resected by initial surgery. Long-term survival was achieved in the five patients with stage IB. In our case with stage IIIB cancer, the patient has been recurrence-free for 14 months since the initial treatment. Therefore, CPT-11 plus S-1 therapy appears to be effective even for the treatment of advanced stage cancer. To the best of our knowledge, this is the first case report of primary signet-ring cell carcinoma of the uterus treated with CPT-11 plus S-1 therapy. We believe CPT-11 plus S-1 therapy to be an effective chemotherapy for signet-ring cell carcinoma of the uterine cervix that is difficult to treat.

Conclusions

We presented a rare case of primary signet-ring cell carcinoma of the uterine cervix. Since signet-ring cell carcinoma is often metastatic, it is necessary to differentiate it from tumor metastasis from other organs. Additionally, CPT-11 plus S-1 combination therapy may be a useful treatment option for signet-ring cell carcinoma of the uterine cervix.

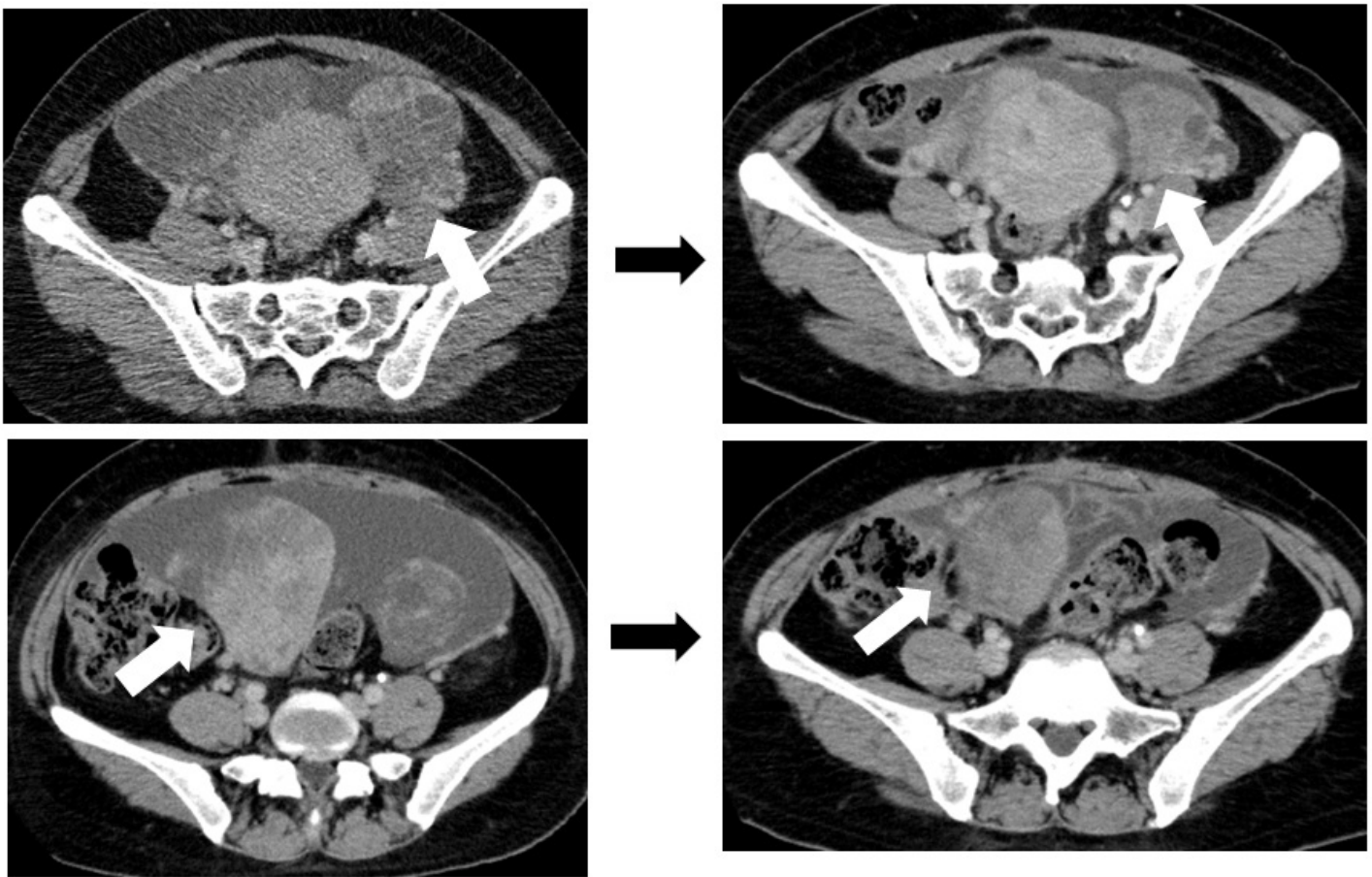


Figure 4. — Computed tomography findings before the start of treatment and after five cycles of CPT-11 plus S-1 therapy. The right ovary shrunk from 15.2 to 6.6 cm and the left ovary from 8.2 to 4.6 cm. The tumor shrinkage rate was 52.2% with partial response of the tumor.

Table 1. — Previous reports of primary signet ring cell carcinoma of uterine cervix.

| | date | age | stage | treatment | chemotherapy | outcome |
|----------------------|------|-----|-------|------------|-----------------------------|----------------|
| Moll UM [5] | 1990 | 50 | III | SX, RT | | NED 10 month |
| Haswani P [1] | 1998 | 68 | III | CCRT | EP | DOD 18 month |
| | | 38 | IB | SX,RT | | NED 9 month |
| Cardosi RJ [6] | 1999 | 53 | IB1 | SX, RT, CT | CDDP | NED 6 month |
| Moritani S [7] | 2004 | 29 | III | SX, CT | TC | NED 6 month |
| Insabato L [8] | 2007 | 46 | IB1 | SX, RT, CT | NA | NED 8 years |
| Lowery WJ [9] | 2009 | 60 | IB1 | RT, SX | | NED > 10 years |
| Veras E [10] | 2009 | 36 | IV | CT | NA | DOD 7 weeks |
| | | 43 | IV | CT | NA | DOD 2 month |
| Yoon A [2] | 2011 | 47 | IB1 | SX | | DAD 6 month |
| Giordano G [11] | 2012 | 45 | IIB | SX | | NA |
| Kaidar-Person O [12] | 2013 | 37 | IIB | CCRT, SX | | NED 4 month |
| Cracchiolo B [13] | 2016 | 64 | IVB | NA | | DOD 3 month |
| Sal V [3] | 2016 | 48 | IB1 | SX | | NED > 18 month |
| Wang YC [14] | 2019 | 48 | IVB | SX, CT | TP 10 cycles + BEV 3 cycles | NED 8 month |

Sx: surgery, CT: chemotherapy, RT: radiotherapy, CCRT: concurrent chemoradiotherapy, NA: not available. EP: Etoposide/Cisplatin, CDDP: Cisplatin, TC: Paclitaxel/Carboplatin, TP: Paclitaxel/Cisplatin, BEV: Bevacizumab.

NED: no evidence of disease, DOD: died of disease.

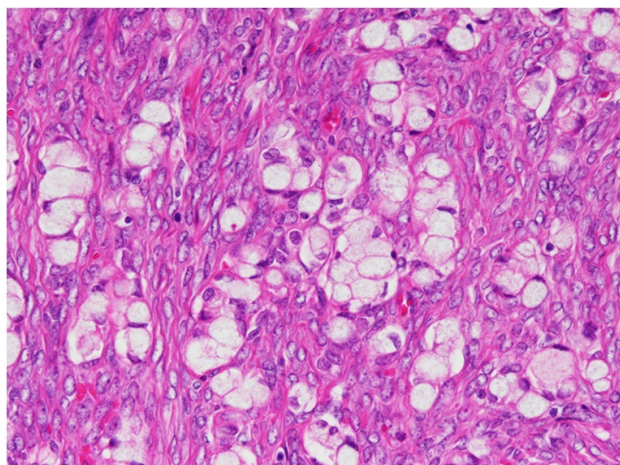


Figure 5. — Left ovary (H&E staining). The left ovarian tumor is solid, and its excised surface is white. Histologically, proliferating and invading signet-ring cell-like atypical cells forming isolated small alveolar structures are noted, which is consistent with signet-ring cell carcinoma.

Ethics Approval and Consent to Participate

This subject gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors report no conflicts of interest in this work.

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