Ovarian Squamous Cell Carcinoma Which Metastasized 8 Years After Cervical Conization for Early Microinvasive Cervical Cancer: A Case Report

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Squamous cell cervical carcinoma that metastasized to the ovary is common in patients with bulky tumors or locally advanced disease; however, ovarian squamous cell carcinoma that metastasized after cervical conization surgery for early microinvasive uterine cervical carcinoma is very rare. We present a case of ovarian squamous cell carcinoma that metastasized 8 years after cervical conization surgery for early microinvasive cervical carcinoma. She had no sign of recurrence in the uterine cervix. We detected human papillomavirus type 16 DNA in both cervical tissue and ovarian tissue, suggesting that ovarian squamous cell carcinoma is derived from microinvasive cervical cancer. Although there are very few cases of early microinvasive squamous cell carcinoma that metastasized to the ovary with delayed recurrence, we should pay attention strictly not only to the cervical condition but also to the ovarian condition on regular post-operative follow-up.

Key words: cervical conization – human papillomavirus – microinvasive cervical carcinoma – squamous cell carcinoma – ovarian metastasis

INTRODUCTION

In reproductive-aged women with early microinvasive cervical squamous cell carcinoma (SCC), fertility-conserving surgery, such as loop electrosurgical excision procedure (LEEP) or cold knife conization, has been proposed as an alternative to hysterectomy. On the basis of the data available in the literature, ovarian preservation could be safely performed in young patients with early-stage SCC. In such patients, however, regular follow-up should be strictly scheduled after surgery.

Cervical cancer metastasis to the ovary is common in patients with bulky tumors or locally advanced disease; however, there appears to be a very low risk of ovarian metastasis in patients with microinvasive SCC (1). We report a very rare case of ovarian SCC that metastasized 8 years after fertility-conserving surgery for early microinvasive SCC. There was no sign of recurrence in the uterine cervix. Human papillomavirus (HPV) examination showed that HPV type 16 DNA was observed in both cervical SCC tissue and ovarian SCC tissue, suggesting that ovarian SCC was a metastasis from microinvasive cervical cancer.

CASE REPORT

A 26-year-old pregnant woman, who desired to preserve the pregnancy, underwent a LEEP cervical conization for CIN 3 during the 10th week of gestation, in January 2001. Because histology of the conization demonstrated microinvasive SCC, non-keratinizing type, with a maximal depth of 2 mm and a width of 4 mm, positive lymphovascular involvement, and positive endocervical margin (Fig. 1a and b), additional LEEP conization and prophylactic cervical cerclage was performed during the 14th week of gestation. Histology did not demonstrate any residual carcinoma, and the patient continued her pregnancy with regular fetal follow-up. At the 37th week of gestation, she was safely delivered of a girl. After delivery, considering positive lymphovascular involvement, we proposed the patient to perform pelvic
lymphadenectomy. However, she refused our offer, and we had no choice but to follow up closely in the outpatient unit with strict control of the cervix, which included repeated colposcopy and cervical cytology, paying attention to lymph node or ovarian swelling, at 3- to 6-month intervals.

Eight years after delivery, she complained of progressive lower abdominal pain, in January 2009. Physical examination demonstrated a low abdominal pelvic mass. Normal appearances of the vulva, vagina and cervix were noted upon pelvic examination. There were no pathological lesions in the ectocervix, and cytology proved negative. Sonographic examination demonstrated a solid-cystic mass measuring 8 × 6 cm. The serum levels of tumor markers were examined, including SCC antigen which showed marked elevation (73 ng/ml). Pelvic magnetic resonance imaging demonstrated a right ovarian solid tumor with marked enhancement. Right common iliac and left external iliac lymphadenopathies were also demonstrated (Fig. 2). Abdominal computed tomography (CT) demonstrated right renal hydronephrosis and hydroureter, and the right glomerular filtration rate was calculated as 8 ml/min by Renogram. However, CT did not demonstrate any possibility of metastatic tumor or tumor derived from other origins. Under a tentative diagnosis of a primary ovarian cancer, exploratory laparotomy was performed in February. At laparotomy, an ovarian tumor measuring about 10 × 9 × 8 cm appeared to be tightly adhered to the posterior layer of the peritoneum including the right ureter and directly invaded the rectum. Therefore, the tumor was carefully removed from the peritoneum, right ureter and rectum. Regrettably, the tumor could not be resected completely, and there were focally positive surgical margins on the rectal surface. Finally, debulking surgery with tumor resection, including bilateral salpingo-oophorectomy, and pelvic lymph-node sampling were finished suboptimally. Grossly, the right ovarian tumor demonstrated a unilocular tumor containing a solid component. Microscopically, it showed a high-grade SCC, and the sampled pelvic lymph nodes were diagnosed positive. Moreover, extensive lymphovascular invasion was noted (Fig. 3). There was no evidence of endometriosis or teratomatous components. Immunohistochemically, the tumor cells were positive for p16 marker (Fig. 4a). Revision of the pathology of the LEEP specimen demonstrated diffuse positive staining for p16 marker (Fig. 4b). Furthermore, HPV DNA type 16 copy numbers were determined in both the cervical tissue (3.3 × 10^4 copies) and ovarian tissue (3.5 × 10^4 copies) by quantitative polymerase chain reaction (PCR). Altogether, these findings resulted in a diagnosis of right ovarian SCC, metastatic from the microinvasive cervical SCC.

Following surgery, the patient underwent adjuvant chemotherapy with paclitaxel (60 mg/m^2) and carboplatin (area under the curve; AUC 2) at 1-week interval for 24 courses and whole pelvic radiotherapy was given in 27 fractions of 2 Gy (total of 54 Gy) till July. After completion of chemotherapy and radiotherapy, the residual tumor dramatically decreased in size and the serum level of SCC antigen decreased to 1.9 ng/ml transiently. However, at the time of follow-up 14 months after debulking surgery, she demonstrated disease progression and the serum level of SCC antigen had increased to 27.3 ng/ml. The patient has received palliative chemotherapy with paclitaxel, and the disease is currently stable.

**DISCUSSION**

Primary SCC is mostly associated with mature cystic teratoma, Brenner’s tumor, mucinous cystadenoma and endometriosis (2,3). However, SCC of the ovary without such lesion appears to be extremely rare. Among tumors that metastasized to the ovary, metastatic SCC originating from the cervix commonly metastasized by direct extension (4). In most of these cases, endometrial or corpus extension was found, suggesting the direct extension.

The risk of ovarian metastasis in FIGO stage IB–IIIB SCC of the uterine cervix is reported to be less than 1% (5). Therefore, this case is very rare, because, the original tumor was microinvasive SCC, and a disease-free condition was maintained for 8 years. There is no doubt that lymphovascular involvement which was identified in the resected conization specimen is an important risk factor for nodal metastases for women with IA1 tumors, and nodal disease is reported in 8% of patients with lymphovascular involvement.
compared with only 0.8% without lymphovascular involvement (6,7). After delivery, we proposed the patient to perform pelvic lymphadenectomy; however, she refused our offer, and we had no choice but to follow up strictly.

In general, cervical SCC is related to an infection with high-risk HPV (HR-HPV). In SCC of the ovary, Mai et al. (8) reported the first ovarian case of SCC that was suggested to show a relation between ovarian SCC and infection with HR-HPV. Thereafter, HR-HPV positivity in SCC of the ovary, associated with cervical squamous intraepithelial neoplasia or cervical SCC in situ, has been reported (8–11). For the detection of HR-HPV, the immunohistochemical result with p16 has been reported to correlate with histologic diagnosis (12). In this case, it was impossible to rule out a primary squamous cell tumor of the ovary completely, especially in a patient with such a long disease-free interval.

**Figure 2.** Pelvic magnetic resonance imaging demonstrating a pelvic solid tumor with marked enhancement. On T1-weighted magnetic resonance imaging, the tumor showed heterogeneous hypointensity. After administration of gadolinium-DTPA, the delayed phased image showed heterogenous tumor enhancement (arrow indicates pelvic tumor).

**Figure 3.** High-grade SCC with extensive lymph-vascular space invasion (arrow indicates focus of lymphovascular involvement) (hematoxylin–eosin stain, original magnification, ×100, a; ×400, b).

**Figure 4.** (a) Immunostaining of the ovarian tumor for p16 marker: the ovarian tumor cells were positive for p16 marker. (b) Immunostaining of LEEP specimen for p16 marker: LEEP specimen also showed diffuse positive staining for p16 marker.
However, the specimens from LEEP conization and from debulking surgery of the ovarian cancer showed immunohistochemically positive staining for p16 marker, suggesting HR-HPV infection in both tissue samples. Furthermore, HPV DNA type 16 copy numbers were determined in both the cervical tissue and ovarian tissue by quantitative PCR, suggesting that ovarian SCC was derived from microinvasive cervical cancer.

The therapeutic approach to SCC of the ovary is controversial. Eltabbakh et al. (13) and Ohtani et al. (14) reported cases that showed a good response to paclitaxel–cisplatin or paclitaxel–carboplatin. However, Shingleton et al. (15) reported cases that did not respond to standard treatment for cervical cancer, including cisplatin and radiotherapy. Optimal surgical debulking might be of importance to survival, as it is for epithelial ovarian cancer in general. This case underwent debulking surgery and treated with adjuvant chemotherapy consisting of paclitaxel and carboplatin, followed by radiotherapy, and a reduction in residual disease along with a slight decrease in serum levels of SCC antigen were detected; however, the patient currently shows progressive disease.

SCC of the ovary presenting in the advanced stages may demonstrate a poorer outcome even after debulking surgery with post-operative chemotherapy and/or radiotherapy. Further clinical investigations are needed to improve the outcome of this disease.

Conflict of interest statement
None declared.

References