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Case Report Open Access

A Case of Ovarian Metastasis from Microinvasive Adenosquamous Carcinoma of the Uterine Cervix

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Abstract

Background: Ovarian metastasis is rare in cases of early-stage uterine cervical cancer. For the patients with stage 1b cervical cancer, the incidences of ovarian metastasis were 0.22% of squamous cell carcinoma and 3.72% of adenocarcinoma. The safety of ovarian preservation is controversial for young women, although these women may find it important to preserve fertility.

Case: A 36-year-old Japanese woman underwent a loop electrosurgical excision procedure for cervical adenosquamous carcinoma with invasion of 0.8 mm in depth and 1 mm in horizontal extent. She wished to preserve her fertility and was therefore followed up without additional treatments. Thirty months after the loop electrosurgical excision procedure, she had 10 cm-diameter ovarian tumors and underwent hysterectomy, bilateral salpingo-oophorectomy, appendectomy. This ovarian tumor was revealed to metastasis from cervical carcinoma.

Conclusion: To our knowledge, this is first reported case of ovarian metastasis with microinvasive adenosquamous cell carcinoma. The pathological characteristics are important for prognosis: frequent small foci of invasion and high atypia.

Keywords: Cervical cancer; Metastasis; Ovarian recurrence; HPV

Case and Method

Ovarian metastasis rarely occurs in cases of early stage uterine cervical cancer. Here, we report a case of an ovarian metastasis that occurred 30 months after primary treatment for microinvasive adenosquamous carcinoma of the uterine cervix.

A 36-year-old Japanese woman was found to have a Papanicolaou smear with atypical glandular cells (AGC) (Figure 1a) and was referred to our hospital. She did not have a history of pregnancy or delivery. A punch biopsy was performed, the pathology of which showed adenocarcinoma in situ of the uterine cervix. She underwent a Loop Electrosurgical Excision Procedure (LEEP). The histological diagnosis was adenosquamous carcinoma with invasion of 0.8 mm in depth and 1 mm in horizontal extent. Lymph-vascular permeation was not identified (Figure 1b). The surgical margin was negative for carcinoma. She wished to preserve her fertility and was therefore followed up without additional treatments.

Thirty months after the LEEP, a 5 cm papillary left ovarian tumor was detected by transvaginal ultrasound examination. Magnetic resonance imaging of the pelvis also showed the papillary ovarian tumor with carcinomatous peritonitis (Figure 2). The tumor markers were as follows: CA 125, 169.1 U/ml; carcinoembryonic antigen, 56.3 ng/ml; and SCC, 0.5 ng/ml.

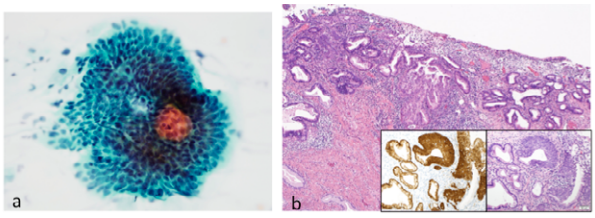

Figure 1: (a) Conventional smear showing a rosette with elongated nuclei. (b) Microscopic Findings (hemotoxylin and eosin stain, immunohistochemical p16): the lower-power appearance of the microinvasiveadenosquamous carcinoma that had invaded greater than 1 mm in depth without lymph-vascular permeation.

She underwent hysterectomy, bilateral salpingo-oophorectomy, appendectomy because of the mucinous feature of the tumor, and low anterior resection of the rectum because of the rectal serosal tumor invasion. Macroscopically, the left ovarian tumor measured 10 cm in the greatest dimension (Figures 3a and 3b). The intraoperative histological diagnosis was mucinous adenocarcinoma with destructive stromal invasion. The remaining uterine cervix was negative for carcinoma. She received six cycles of adjuvant chemotherapy (SOX: oxaliplatin 100 mg/m^2, day 1; TS-1 80-100 mg/body, days 1-14). Additionally, the LEEP specimen was re-examined. The immunohistochemical profiles were same among the uterine cervical carcinoma, ovarian carcinoma, and disseminated tumor of the peritoneum. These tumors were positive for mucin 5AC (strongly), mucin 6 (weakly), cytokeratin 20 (weakly), p16 (strongly). They were negative for CDX2 and CD10.

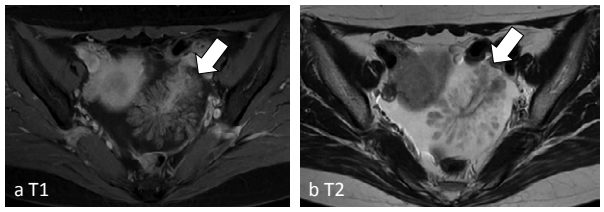

Figure 2: T1-weighted magnetic resonance image showing the papillary left ovarian mass.

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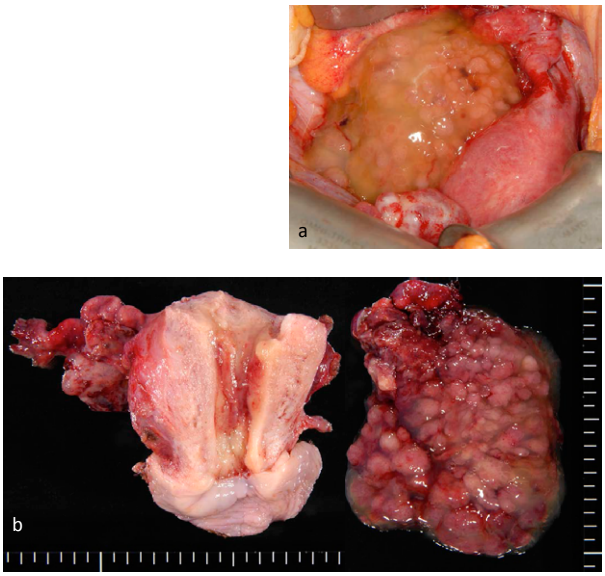

Figure 3: (a) Laparotomy findings: papillary left ovarian mass with mucin. (b) Macroscopic findings: the uterine cervix had no remaining tumor after the loop electrosurgical excision procedure (LEEP), and right ovary was a normal size.

Histological examination	Adenosquamous cell carcinoma	mucinous adenocarcinoma
In situ hybridization	Dot	Dot
IHC		
p16	+	+
CK20	+	+
MUC5AC	+	+
MUC6	+	+
CDX2	–	–
CD10	–	–
KRAS	–	–
HPV typing test	18	18

LEEP: Loop Electrosurgical Excision Procedure; CK20: Cytokeratin 20

Table 1: Characteristics of the specimen LEEP specimen Ovarian tumor the portion of dissemination.

Ki-67 labeling index was over 90%. Subsequently, Human Papilloma Virus (HPV) was investigated using in situ hybridization and HPV typing test. The in situ hybridization assessment of high-risk human papillomavirus showed dot-like nuclear positivity in each tumor and HPV18 type is detected by HPV typing test (Clinichip HPV test that detects carcinogenic human papillomavirus rapidly by loop-mediated isothermal amplification and performs genotyping of 13 carcinogenic types using automated DNA chip technology, microdissected formalin-fixed and paraffin-embedded tissue). The LEEP specimen, ovarian tumor, and the disseminated tumor each contained wild type KRAS. The clinicopathological features of the case are summarized in Table 1 and Figure 4.

Based on these findings, the final diagnosis of the ovarian tumor was metastasis from cervical carcinoma. Twelve months after the recurrence, the patient is alive and without evidence of disease.

Discussion

Early stage uterine cervical carcinoma is increasingly detected by cytological screening. Ovarian preservation has been considered for young patients and, indeed, the preservation of fertility is an important issue for young women with uterine cervical carcinoma.

Ovarian metastasis is rarely present at the time of initial treatment in patients with early stage uterine cervical carcinoma. A review by Landoni et al. showed that ovarian metastasis from stage 1a2-2a cervical cancer occurred in 0.5% (7/1283) of squamous cell carcinoma cases and 2.4% (9/380) of adenocarcinoma cases [1]. In a Japanese population of patients with stage 1b cervical cancer, the incidences of ovarian metastasis were 0.22% (4/1784) of squamous cell carcinoma and 3.72% (14/376) of adenocarcinoma [2]. The preservation of ovarian function is often feasible for patients with squamous cell carcinoma, but it is not feasible for patients with adenocarcinoma.

Moreover, metastasis to the ovary is rare, especially in cases of early microinvasive uterine cervical carcinoma [3-5]. Ostor et al. described 155 patients with early invasive adenocarcinoma (defined as a depth of invasion of 5 mm or less), none of whom had ovarian metastasis [6]. In previous studies, the risk factors for ovarian metastasis from cervical carcinoma were found to be histologic type (adenocarcinoma), lymph-vascular space invasion, age (>45 years old), and International Federation of Gynecology and Obstetrics stage [1,4,7,8].

Ovarian metastasis is also rare as a recurrence of cervical carcinoma. Table 2 provides a summary of the previous reports on this topic [4,8-10]. Some cases were ovarian metastasis in a transposed ovary in patients treated for cervical cancer. The patients were treated for stage 0-1b disease. These studies indicated that p16 and human papillomavirus in situ hybridization would be useful for distinguishing between metastasis from cervical carcinoma and primary ovarian carcinoma. Immunohistochemistry and human papillomavirus in situ hybridization played key roles in the differential diagnosis of this case.

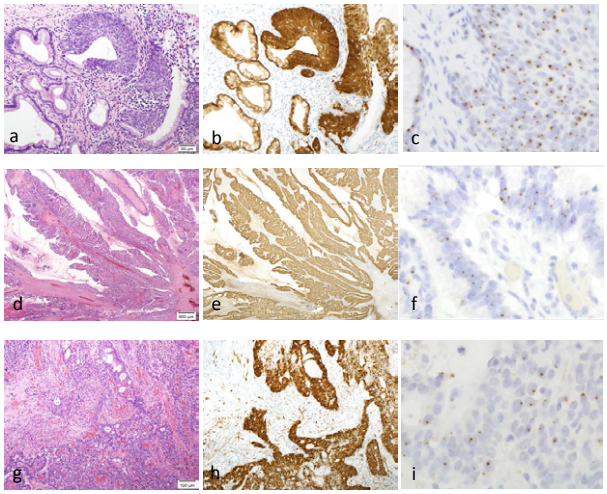

Figure 4: (a) Histological findings of the loop electrosurgical excision procedure (LEEP) specimen. The tumor was adenosquamous carcinoma. (b) Immunohistochemically, LEEP specimen showed diffuse and strong positivity for p16. (c) In situ hybridization for high-risk human papillomavirus (wide spectrum HPV, DAKO), showing dot-like nuclear positively. (d) Histological feature of the left ovarian tumor. The findings were compatible with mucinous adenocarcinoma. (e) Immunohistochemically, the ovarian tumor showed diffuse and strong positivity for p16. (f) In situ hybridization for high-risk human papillomavirus, showing dot-like nuclear positively. (g) Histological findings of disseminated tumor. The tumor was adenocarcinoma with squamoid feature. (h) Immunohistochemically, disseminated tumor showed diffuse and strong positivity for p16. (i) In situ hybridization for high-risk human papillomavirus, showing dot-like nuclear positively.

Reference	Age	Cervical cancer		Depth of Invasion	Horizontal Extent	Ovarian metastasis		Follow up
		Stage	Histological type			Time to recurrence	Histological type	
Janse [8]	43	1B1	AS	NA	NA	10y	AS	3y NED
Morice [9]	34	1B1	SCC	NA	NA	3y	NA	15M DOD
	34	1B1	SCC	NA	NA	3y	NA	1M NED
Delotte [10]	36	1B1	adeno	NA	35 mm	2y	adenocarcinoma	5y NED
Ronnett [4]	34	1A	adeno	3 mm	9 mm	13M	Endometrioid (borderline)	51M NED
	45	1A	adeno	7 mm	15 mm	6y	mucinous	24M AWD
	28	1B1	adeno	4 mm	21 mm	28M	mucinous	54M AWD
	38	0	AIS	NA	NA	6y	NA	35M DOD

Table 2: Summary of reported cases of ovarian metastasis in primary cervical cancer (stage 0-1b).

The evaluated HPV-related tumors showed diffuse/strong expression of p16. These examinations revealed carcinoma related to human papillomavirus. No mutation was detected in the *KRAS* gene. In our case, the macroscopic findings of ovarian tumor with mucin on the surface were unique. The somewhat different histological features of cervical adenosquamous carcinoma, and ovarian tumor had confused us.

To our knowledge, this is first report of ovarian metastasis with microinvasive adenosquamous carcinoma. Previous reports have shown ovarian metastasis with cervical adenocarcinoma that was stage 1a. National Cancer Institute guidelines do not specify a separate treatment for each histological type, even though cervical adenocarcinoma was more likely to lead to ovarian metastasis than was squamous cell carcinoma. Furthermore, adenosquamous cell carcinoma should be considered in this point. In this case, the histological findings showed differentiated adenocarcinoma in situ, squamous cell carcinoma in situ with glandular involvement, and some nests of adenosquamous carcinoma in an invasive lesion. Further, ovarian metastasis had occurred from a microinvasive adenosquamous carcinoma that included small foci of invasion (less than 1 mm) and did not include lymph-vascular permeation. Even though the invasion appeared to mimic, the case was inexplicably ovarian metastasis.

Conclusion

Ovarian metastasis is rare in cases of early-stage uterine cervical cancer. The safety of ovarian preservation is controversial for young women, although these women may find it important to preserve fertility. Although the tumor's histological type, extension, and pattern of invasion should be considered, cases should not be overtreated. We suggest that the following pathological characteristics are important for prognosis: frequent small foci of invasion and high atypia.

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