CASE REPORT

A case of adenocarcinoma of the endometrial type mixed with a clear cell component that metastasized to the vagina

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Summary

We present a patient with adenocarcinoma of the endometrial type mixed with a clear cell component (AMC) that metastasized to the vagina and one of the pelvic lymp nodes. She underwent a radical hysterectomy and pelvic and paraaortic lymphadenectomy, and then received postoperative adjuvant chemotherapy. Histologic features of the endometrial tumor included clear cell adenocarcinoma with an approximate 10% extent to endometrioid adenocarcinoma. On the other hand, histologic examination on the vaginal tumor predominatly showed clear cell adenocarcinoma and also revealed endometrioid adenocarcinoma to a very small extent, suggesting metastasis to the vagina from AMC. On immunohistochemical examination, expression of vascular endothelial growth factor (VEGF)-A, VEGF-C and VEGF-D was apparently stronger in the component of clear cell adenocarcinoma than in that of endometrioid adenocarcinoma. She has been a disease-free survivor for 26 months. Interestingly, locations of endometrial and vaginal lesions were consistent with the sites of an intrauterine device and ring pessary insertion, respectively.

Key words: Adenocarcinoma of the endometrial type mixed with a clear cell component; Vaginal metastasis; Intrauterine device; Ring pessary; VEGF.

Introduction

Solitary metastasis of endometrial adenocarcinoma to the vagina is extremely rare. Nicklin and Petersen reparted that 14 (0.7%) of 1,940 patients with endometrial adenocarcinoma had Stage IIIB disease [1]. However, it is likely that most of the patients diagnosed with Stage IIIB disease were spuriously understaged because they did not undergo a full surgical staging procedure due to their poor medical condition, suggesting that the real rate of Stage IIIB disease is less than that reported. The pathogenesis for vaginal metastasis is inferred to be caused by lymphatic embolization from the primary tumor site [2]. Therefore, it is interesting to argue that metastasis of endometrial adenocarcinoma to the vagina will be simultaneous with lymph node metastasis.

We present here a patient with adenocarcinoma of the endometrial type mixed with a clear cell component (AMC), a rare type of endometrial carcinoma [3] that metastasized to both the vagina and one of the pelvic lymph nodes. This patient had an intrauterine device (IUD) and ring pessary for management of uterine prolapse, and showed interesting features on the sites of the primary and metastatic lesions. In addition, we referred to distinctive features of immunohistochemical staining for the vascular endothelial growth factor (VEGF) family in endometrioid and clear cell components.

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Case Report

A 67-year-old woman, gravida 3 para 3, complained of atypical genital bleeding in September 2000 that had continued for one month. The ring-pessary had been taken out at a private clinic one month before her visiting our clinic. A cervical smear taken at that time had been normal. Her last menstrual period was at the age of 50. The patient's previous medical history was unremarkable.

A pelvic examination revealed an enlarged uterine body with a myoma node 6 cm in diameter and a normal uterine cervix. Three polypous lesions, which bled easily, were found on the vaginal wall near the posterior fornix. The location of those lesions was consistent with the site of the ring pessary. A smear of the vaginal lesions revealed aggregated tumor cell clusters with irregular margins and a partial sheet-like arrangement including large nuclei with anisonucleosis, prominent nucleoli, and abundant clear cytoplasm on a necrotic background, suggesting existence of clear cell adenocarcinoma. The biopsy histologic type from the lesions was clear cell adenocarcinoma with hobnail-like cells. Furthermore, a smear from the endometrium suggested existence of adenocarcinoma and the biopy indicated grade 2 endometrioid adenocarcinoma. Computed tomography of the abdomen and pelvis revealed no evidence of disease except for the uterus. Thus, her disease was rated as concurrent endometrial and vaginal adenocarcinoma and she underwent a radical hysterectomy and pelvic and paraaortic lymphadenectomy in December 2000.

Coexistence of endometrial and vaginal tumors was confirmed in the surgically resected specimen (Figure 1). An IUD was unexpectedly found in the uterine cavity (Figure 1). It had been placed about 30 years before. Histologic features of the endometrial tumor included clear cell adenocarcinoma with an approximate 10% extent to endometrioid adenocarcinoma (Figure 2). On the other hand, histologic examination of the

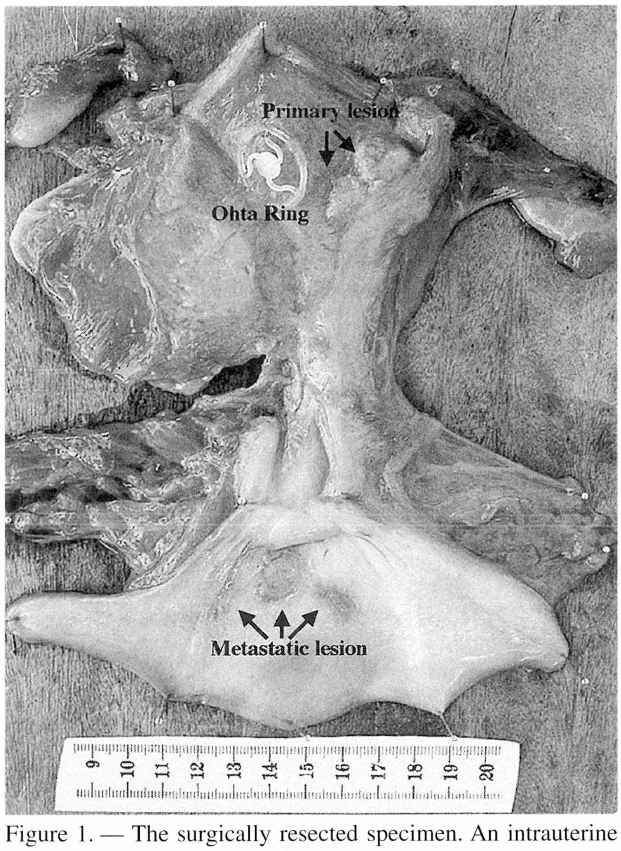

Figure 1. — The surgically resected specimen. An intrauterine device (Ohta ring) was found in the uterine cavity.

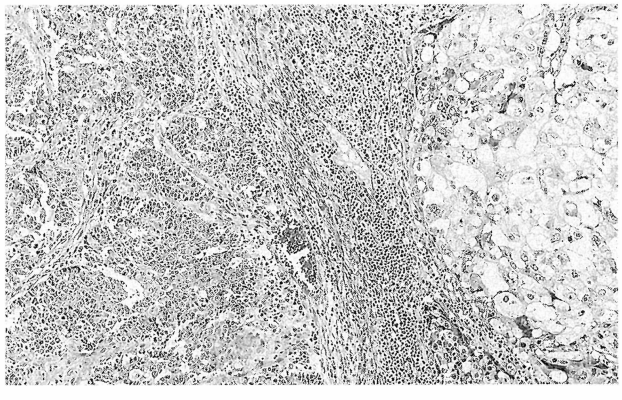

Figure 2. — Histologic features of the endometrial lesion. The components of endometrioid adenocarcinoma, G2 grade and clear cell adenocarcinoma can be observed (Haematoxylin and eosin, original magnification x 100).

vaginal tumor predominantly showed clear cell adenocarcinoma and also revealed coexistence of endometrioid adenocarcinoma to a small extent (Figure 3), suggesting metastasis to the vagina from AMC. She received postoperative adjuvant chemotherapy consisting of CDDP 60 mg/m^2, epirubicin 30 mg/m^2 and cyclophosphamide 300 mg/m^2 and has been disease-free for 26 months.

Expressions of the VEGF family that were related to tumor invasion and metastasis were examined immunohistochemically [4-6]. Sections 6 μm thick were stained for VEGF-A, VEGF-C and VEGF-D by the LSAB kit (DAKO, Santa Barbara, CA) using anti-VEGF-A antibody (Santa Cruz Biotechnology, Santa Cruz, CA), anti-VEGF-C antibody and anti-VEGF-D antibody (R&D Systems, Abingdon UK), as reported previously [7]. Immunohistochemical examination of the primary endometrial tumor revealed that expression of VEGF-A, VEGF-C and VEGF-D was apparently stronger in the component of clear cell adenocarcinoma than in theat of endometrioid adenocarcinoma (Figure 4).

Discussion

AMC is reported to make up only 1.8% of endometrial adenocarcinomas [3]. The prognosis is significantly poorer in AMC than in endometrioid adenocarcinoma and there is no difference in outcome between patients with AMC and pure clear cell adenocarcinoma [3]. The metastatic lesion of the vagina in this case revealed a predominant component of clear cell adenocarcinoma although the component was a very small quantity in the primary endometrial lesion, suggesting that the clear cell component was profoundly related to the patient's prognosis. Immunohistochemical examination of the primary endometrial tumor revealed that expression of the VEGF family was apparently stronger in the component of clear cell adenocarcinoma than in that of endometrioid adenocarcinoma. Our previous studies clarified a significant association between

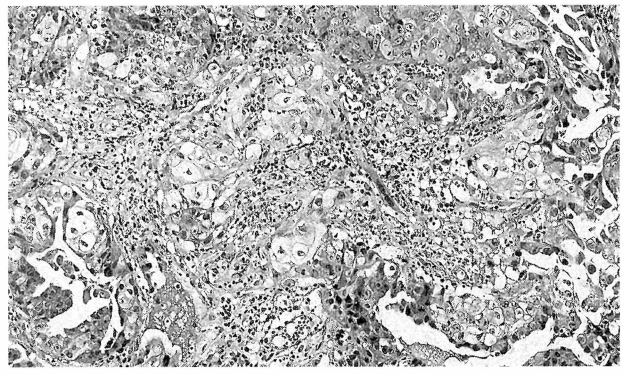

Figure 3. — Histologic features of the metastatic vaginal lesion. The component of clear cell adenocarcinoma can be predominantly seen (H&E, original magnification x 100).

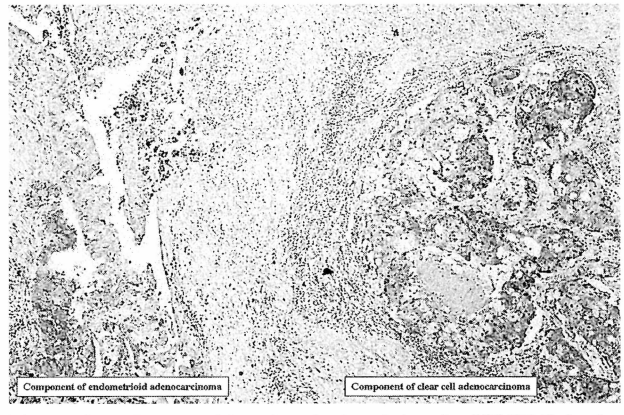

Figure 4. — Immunohistochemical staining for VEGF-D in the endometrial lesion. The expression of VEGF-D was stronger in the clear cell adenocarcinoma than in the endometrioid adenocarcinoma (original magnification x 40).

increased expression of the VEGF family and lymph node metastasis in endometrial and ovarian carcinoma [4-6]. These results could explain the above-mentioned histologic feature that the clear cell adenocarcinoma component had a higher potential in metastasis.

MacKillop and Pringle noted that vaginal metastases usually occurred in the absence of macroscopic evidence of cervical disease [2]. The most likely pathogenesis for vaginal metastasis is lymphatic embolization from the primary tumor [2]. Endometrial malignancy has a proven tendency to penetrate, embolize and metastasize along lymphatic channels to the vagina and to the retroperitoneal lymph nodes [1]. Thus, vaginal metastasis from an endometrial lesion might be almost simultaneous with lymph node metastasis. In fact, Nicklin and Petersen reported that most of endometrial carcinomas with vaginal metastasis concurrently involved lymph node metastasis and just 0.7% of 1,940 patients with endometrial adenocarcinoma had solitary metastasis to the vagina [1]. However, the stage of theses patients diagnosed as Stage IIIB endometrial adenocarcinoma could not be determined by a full surgical staging procedure due to their poor medical condition [1]. The incidence of solitary metastasis to the vagina from an endometrial tumor site may be much lower than our expectations.

Interestingly, in this case, locations of endometrial and vaginal lesions were consistent with the IUD and ring pessary insertion sites, respectively. There are a few reports that endometrial carcinomas were induced by the prolonged use of an IUD [8, 9]. The prolonged mechanical stimulus of the inserted IUD was presumed to be responsible for carcinogenesis and the long-term use of an IUD was inferred to play an important role as a co-carcinogen [8]. On the other hand, some authors have reported a protective effect of IUD use on endometrial cancer risk [10-12]. Benshushan *et al.* described that IUD use might decrease the risk of endometrial cancer through the intense inflammatory response that leads to other lisosomal actions which may include cells responsible for early elimination of hyperplastic endometrial epithelial cells and through the more complete shedding of the endometrium associated with IUD use [10]. However, recently occurrence of endometrial carcinoma following IUD use has been reported [13]. The association between IUD use and the risk of endometrial cancer is not yet conclusive. Schraub *et al.* reported 28 untreated primary vaginal carcinomas associated with a history of vaginal pessary use to control uterovaginal prolapse [14]. They concluded that foreign body chronic inflammation in association with viral infection might be the cause of the vaginal tumors because almost all of those tumors occurred at the site of pessary insertion [14]. Histological type of the vaginal tumors in relation to ring pessary has been reported to be predominantly adenocarcinoma [14]. Although there is no evidence of whether IUD and ring pessary has led to malignancies, prolonged unnecessary use of these devices should be avoided.

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