Case Report
Primary vaginal clear cell adenocarcinoma accompanied by Herlyn-Werner-Wunderlich syndrome without prenatal diethylstilbestrol exposure: a case report

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Abstract: We report a rare case of a 40 years old woman with primary vaginal clear cell adenocarcinoma (CCA) accompanied by Herlyn-Werner-Wunderlich syndrome (HWWS) and without any prenatal diethylstilbestrol exposure. Pathological results indicated that the CCA was surrounded by adenosis and that there was a benign to malignant transformation of several glands in the epithelium, so the CCA was believed to have arisen from the adenosis. The literature review disclosed that genitourinary anomalies might be associated with an increased risk of adenocarcinoma, but the mechanism was not clear.

Keywords: Clear cell adenocarcinoma (CCA), diethylstilbestrol, genitourinary malformation, Herlyn-Werner-Wunderlich syndrome, vaginal adenosis

Introduction
Primary vaginal malignant tumors account for only 1% to 3% of all malignant tumors of the female reproductive tract [1]. Primary vaginal adenocarcinoma is rare, and the most common histologic type is clear cell adenocarcinoma (CCA) [2]. This tumor gained recognition in the 1970s because of its association with intrauterine exposure to diethylstilbestrol (DES) [3, 4]. Vaginal adenosis, defined as the development of columnar epithelium in the vagina, is the most common anomaly in women exposed to DES in utero. Currently, it is widely accepted that adenosis is a precursor of CCA [5].

Congenital malformations of the female genital tract are defined as deviations from the normal anatomic structure due to embryological maldevelopment of the Müllerian or paramesonephric ducts. This is a very common benign disease with a prevalence of 4% to 7% in the general population [6]. Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare congenital anomaly characterized by uterus didelphys with a blind hemivagina and ipsilateral renal agenesis, and is responsible for 7.1% of all female genital tract abnormalities [7]. Primary vaginal CCA accompanied by HWWS is rare and fewer than 5 cases have been reported [1, 8]. Herein, we reported a case of primary vaginal CCA accompanied by HWWS, which is considered to be derived from coexisting adenosis without intrauterine DES exposure.

Case report
A 40-year-old Chinese woman with gravidity 1, parity 1 through Caesarean section complained of abnormal vaginal bleeding for 4 years. The manifestation was the elongation of the menstruation period from 7 days to more than 10 days and an increase in menstrual volume. A vaginal left oblique septum with a hole of approximately 1 cm in diameter was discovered upon inspection, and there was a little clear liquid flowing out of the hole. The right cervix was smooth, but the cervix behind the oblique septum could not be detected. Transvaginal ultrasound revealed two uterine bodies and cer-
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vical canals. MRI detected two separate uterine bodies and cervical canals, and there were no abnormalities in the uterine cavities and cervixes (Figures S1, S2 and S3). The upper segment of the left vagina was thickened, and the signal of left fornix was abnormal. The urinary tract ultrasound revealed agenesis of the left kidney. The cytologic examination of the right uterine cervix was negative for intraepithelial lesions or malignancies (NILMs). The initial diagnosis was HWWS and abnormal uterine bleeding.

During the oblique vaginal septum resection, the left uterine cervix and a 2×1 cm rough lesion in the left fornix were revealed. Pathologic diagnosis of the oblique septum and the left fornix lesion found clear cell adenocarcinoma. The schematic of the abnormalities and lesions is shown in Figure 1. Cytological examination of the left uterine cervix indicated NILM, and biopsy of the endometrium from both uterine cavities revealed endometrium in the proliferative stage. The patient had no prenatal DES exposure. Three weeks later, radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy were performed based on a diagnosis of stage I vaginal CCA.

Microscopically, CCA was found in the upper segment of the vagina and vaginal oblique septum. As shown in Figure 2, the CCA lesion was surrounded by adenosis, and there was a benign to malignant transformation of several glands in the epithelium, so the CCA was considered to have arisen from the adenosis. The tumor involved the vaginal cuff and the lymphovascular space. There was no tumor involvement in the parametrium, ovaries, fallopian tubes, pelvic lymph nodes, or lateral surgical borders. Meanwhile, there was adenomyosis in the left corpus uteri but not in the right corpus uteri. Because of the positive vaginal cuff and lymphovascular space invasion, adjuvant radiotherapy and chemotherapy were administered. The patient is still alive at 17 months after the surgery.

Discussion

In adult women, the incidence of non-DES-induced vaginal adenosis was about 10% [9]. In addition to the toxicity of DES exposure, chemotherapeutic drugs such as 5-fluorouracil might also promote the occurrence of vaginal adenosis and cancer [10, 11]. In our case, the patient had not been exposed to DES or any chemotherapy, so it was hypothesized that the adenosis might have arisen from maldevelopment of the Müllerian duct, but this speculation lacked supporting evidence. Uehara et al. [1] reported a case of vaginal CCA with adenosis accompanied by a bicornuate uterus. There-
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Therefore, it is necessary to further identify similar cases in order to investigate whether vaginal adenosis coexists with or is caused by urogenital abnormalities. Our patient received a final diagnosis of genital tract malformation and vaginal CCA approximately 4 years after the onset of symptoms, which lasted until the oblique septum was removed. Making the correct diagnosis seemed more difficult in women with reproductive tract abnormalities than in those without such malformations. First, irregular vaginal bleeding is a common symptom of lower genital tract tumor and genital tract abnormalities and the clinical manifestations might be atypical. Additionally, for patients with HWWS, the gynecological exam usually cannot discover a tumor which is located in the blocked cervix or vaginal wall. Zong et al. [12] conducted a retrospective study of 36 women diagnosed with lower genital tract primary carcinoma accompanied by genitourinary abnormalities. It was found that 69.4% of the analyzed patients with genitourinary tract malformations had adenocarcinoma of the lower genital tract. This suggested that genitourinary anomalies were associated with an increased risk of adenocarcinoma, but the mechanism was not clear. A study [13] indicated that teratogenic factors might make the Müllerian epithelium more sensitive to a carcinogenic substance.

In our study, the follow-up time was not long enough. Another study found that the 5-year survival rates in women with stage I and II non-DES-associated vaginal adenocarcinoma were 80% and 25% respectively. These outcomes were inferior to those of patients with DES-associated vaginal CCA [14].

Disclosure of conflict of interest

None.
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References


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Figure S1. T2W TSE coronary image showing the two uterine bodies.

Figure S2. T2W SPAIR sagittal image showing the right uterus.
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Figure S3. T2W SPAIR sagittal image showing the left uterus.