Clear Cell Adenocarcinoma of the Uterine Cervix

Chun-Wei Chen[1], Hseng-Mou Hsiao[1], Chi-An Chen[1], Chang-Yao Hsieh[1], Wen-Fang Cheng[1,2]*

[1]Department of Obstetric and Gynecology, and [2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan.

Squamous cell carcinomas (SCCs) account for approximately 80% of cervical cancers, adenocarcinomas 15% and adenosquamous carcinomas 3% to 5%. There are some rare variants of malignancy arising from the uterine cervix, such as neuroendocrine or small cell carcinomas, rhabdomyosarcoma in adolescents and young women, and primary cervical lymphoma and sarcoma.

The major risk factors for cervical cancer include early onset of sexual activity, multiple sexual partners, and a high-risk sexual partner. These factors imply the probability of human papillomavirus (HPV) infection, and HPV is strongly associated with the development of cervical cancer. HPV 16 is the dominant type in SCC; however, HPV 18 is more frequently seen in adenocarcinoma [1,2]. Other risk factors are a history of sexually transmitted diseases, smoking, high parity, immunosuppression, low socioeconomic status, prolonged use of oral contraceptives, and a previous history of vulvar or vaginal squamous dysplasia.

Disease stage is the most important prognostic factor of cervical cancer, followed by lymph node status. Women with stage IB or IIA disease with negative pelvic lymph nodes have a 5-year survival of 88% to 96%, compared with 64% to 74% for those with similar stage of disease and pelvic nodal metastasis [3]. Some series support that adenocarcinomas have the same 5-year survival rate when adjusted for stage [4–6]. However, other studies also pointed out the higher rate of distant metastases in patients with adenocarcinoma [7].

Clear cell adenocarcinoma (CCAC) accounts for approximately 3% to 10% of adenocarcinomas of the uterine cervix [8]. Primary cervical CCAC generally occurs in young women with *in utero* exposure to diethylstilbestrol (DES), which is prescribed to pregnant women to prevent abortion [9,10]. Here, we present a case of CCAC of the uterine cervix without such a predisposing factor.

A 62-year-old, gravida 2, para 2, postmenopausal woman denied any major systemic disease, such as hypertension, diabetes or cardiac disease. She had never received any Pap smear before. She visited the gynecologic clinic because of painless menopausal bleeding for 1 month. A indurated cervical tumor was noted. Pap smear and cervical biopsy were performed. The result of cervical cytology was normal. However, the histopathology by punch biopsy revealed CCAC. The patient could not recall any *in utero* exposure to DES even though she was thoroughly questioned. She was then referred to our hospital. Pelvic examination showed a uterus in the atrophic state with no obvious cervical lesion, except for the biopsy wound. Bilateral parametria were free of tumor invasion as determined by pelvic examination. Levels of the tumor markers were all within normal ranges: CA-125 22.3 U/mL (normal, < 35 U/mL) and CEA 0.69 ng/mL (normal, < 2.5 ng/mL). HPV test was performed with cervical scraping, and it revealed positive HPV type 18. Pelvic and abdominal magnetic resonance imaging showed a solid cervical tumor around 1.5 cm in diameter. No definite hydronephrosis or abnormal enlarged pelvic or para-aortic lymph nodes could be identified. Cystoscopy revealed no evidence of tumor invasion of the urinary bladder. The patient underwent a radical abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection under the impression of stage IB1 cervical CCAC. A 2-cm tumor inside the posterior cervical wall with intact endocervical canal was identified macroscopically. The pathologic report showed a CCAC composed mainly of marked dysplastic cells with clear or eosinophilic cytoplasm and focally present hobnail nuclei arranged in a tubulocystic pattern (Figure A). Hyaline globules could be noted focally. Perivascular invasion was also seen (Figure B). All of the pelvic lymph nodes were free from tumor metastasis. The bilateral parametria and vaginal cuff were also not invaded by the tumor. Because of the deep stromal and

*Correspondence to: Dr Wen-Fang Cheng, Department of Obstetrics and Gynecology, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: wenfangcheng@yahoo.com
Accepted: June 26, 2007

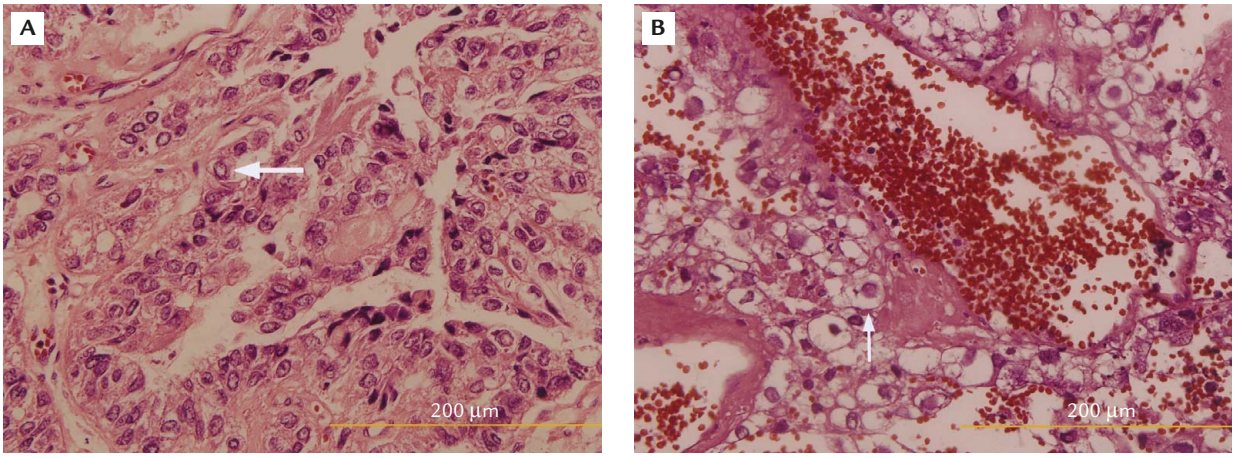

Figure. (A) Marked dysplastic cells with clear or eosinophilic cytoplasm and focally present hobnail nuclei (arrow) arranged in a tubulocystic pattern. (B) Clear cell adenocarcinoma with perivascular invasion (arrow) was also noted. (A, B: hematoxylin and eosin, 400×.)

perivascular invasion, adjuvant radiotherapy was given. She was followed up at our clinic and lived without disease for 6 months.

CCAC is a rare variant of cervical malignancy. CCAC may involve any organ, from ovary to vagina. It is thought to be related to *in utero* exposure of DES, which is prescribed to pregnant women to prevent abortion. However, CCAC does occur without *in utero* exposure to DES. Hanselaar and colleagues reported that among 73 cases of CCAC born after 1947, there were 26 (32%) without exposure to DES [11]. The age distribution showed two peaks. One was at the young age ranging from 17 to 37 years (mean, 26 years), and the other at the older age ranging from 44 to 88 years (mean, 71 years). This bimodal age distribution was attributed to the cases with DES exposure at the first peak. However, in Japan, where DES has not been prescribed to pregnant women, the age at diagnosis ranged from 0 to 79 years with a mean age of 50.8 years, and there were no separate peaks in the age distribution [12]. The age at diagnosis in our case was 63 years. There was no obvious history of the exposure to DES for our patient.

In addition to *in utero* exposure to DES, HPV infection [13], bcl-2 protein overexpression [14] and *p53* gene mutation [15] are also important. Waggoner et al reported HPV type 31 infection detected in cases of CCAC of the vagina and cervix. However, the importance of this infection was not elucidated. Our patient was infected with HPV type 18. This correlated with the most prevalent type observed in cervical adenocarcinoma [1,2], but not with Waggoner et al's observation. Waggoner et al also found p53 protein expression in 14 of 21 cases (67%). It was suggested to be a response to generalized DNA damage. On the other hand, bcl-2 overexpression was observed in 18 of these 21 patients. Their hypothesis supported that overexpression of bcl-2 can inhibit p53-mediated apoptosis and suggests a mechanism by which these rare tumors can arise without mutation of the *p53* gene.

Management of early-stage cervical adenocarcinoma includes radical hysterectomy plus pelvic lymphadenectomy or definitive radiation therapy. High-risk factors for recurrence include positive pelvic lymph nodes, positive parametrial extension, and positive vaginal margins. In patients with these high risk factors, chemoradiation is the postoperative adjuvant treatment of choice [16]. In patients with at least the two following risk factors, postoperative radiation therapy could decrease recurrent rate with acceptable morbidity: capillary lymphatic space invasion with more than one-third stromal invasion, and larger tumor [17].

Stage, tumor size, growth pattern, nuclear atypia, and mitotic activity are important prognostic factors [11]. An unfavorable prognosis is associated with high stage, a large tumor, nuclear atypia, and high mitotic activity. In cervical adenocarcinoma, most of the patients were diagnosed at stage I or II, but their 5-year survival rate was only 55.7% and was poorer than that of the SCC counterparts. Reich et al analyzed 15 CCACs in women not exposed to DES *in utero* [18]. The clinicopathologic findings and prognosis of these patients were similar to those with SCCs and non-CCAC. However, the incidences of parametrial involvement and metastatic pelvic lymph node were 40% and 47%, respectively. Early recurrence and distant metastasis were observed in patients with positive pelvic nodes. There were two risk factors (i.e. lymphovascular permeation and deep stromal invasion) for our patient after radical hysterectomy, and she underwent adjuvant radiotherapy. Although there is no definitive evidence showing a poorer prognosis of CCACs than SCCs, early recurrence

and distant metastasis have been observed. We recommend that patients with cervical CCAC should be treated more aggressively.

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