# Cervical adenocarcinoma with clear cell morphology. Report of six cases and literature review

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**Summary**

Clear cell cervical adenocarcinoma (CCA) is a rather rare malignancy of the genital tract. We report six cases of CCA, diagnosed in our laboratory during a 15-year period: five patients with sporadic primary CCA and one young patient with CCA and a history of in utero exposure to DES. The possible DES exposure, clinicopathological findings as well as the differential diagnosis and the the prognosis of such patients are presented in a mini-review of the literature.

*Key words:* Cervix; Adenocarcinoma; Clear cell cancer.

## Introduction

Adenocarcinomas of the uterine cervix comprise a heterogeneous group of neoplasms that account for 15-25% of cervical carcinomas and display a variety of clinical features and histological patterns [1].

Clear cell adenocarcinoma (CCA) of the cervix is a rare subtype with main pathological characteristics of clear cell morphology, distinct pathogenesis and characteristic clinicopathological features [2].

The first case report of a CCA was made by Meyer in 1903 [3]. However, according to the recently established criteria [4], the morphology and location of this first reported CCA is more consistent with a mesonephric tumour.

This misconception that clear cell and mesonephric carcinomas of the cervix and vagina are one and the same tumour is responsible for the wrong classification of most of the reported cases and the lack of reliable statistical data.

The establishment of the Registry of Clear Cell Adenocarcinomas of the Genital Tract in Young Females in 1974 [5] proposed a new classification of cervical tumours, establishing clear cell carcinoma as a distinct category, different than the mesonephric lesions. The current classification of Uterine Cervical Tumours by WHO (2003) [4] is shown in Table 1.

Clear cell adenocarcinomas develop either as spontaneous tumours in older women (mean age 47 years), or in young women (mean age 19 years) after in utero exposure to nonsteroidal estrogens, particularly diethylstilbestrol (DES) [6]. Between these two subtypes of CCA there are differences in pathogenesis, certain clinical characteristics as well as the prognosis [6]. In older women, CCA develops in the endocervix and the prognosis is similar to the usual infiltrating squamous cell cervical carcinomas. The pathogenesis is unclear and endometriosis is strongly implicated [7,8]. On the other hand, in young women with DES-associated CCA the tumours are located in the ectocervix, there is an association with vaginal adenosis, and the prognosis is considered to be excellent, with 10-year survival reaching 85% [5, 9]. More than 60% of the reported cases of CCA in the later decades of the 20th century could be linked to DES exposure [6], whereas DES-unrelated cases account for 5% of cervical adenocarcinomas [10].

We report six cases of CCA diagnosed in our laboratory during a 15-year period: five patients with sporadic primary CCA and one young patient with CCA and a history of in utero exposure to DES. Furthermore, we performed a mini-review the current literature in the field, and the problems in the differential diagnosis from other lesions with clear cell morphology are discussed.

## Material and Method

During the last 15-year period (January 1995-December 2009) in the Pathology Laboratory of Aretaieion University Hospital, Athens Medical School, 61 cases of infiltrating cervical carcinomas were examined including: 40 cases of squamous cell carcinoma (65.5%), 17 cases of endocervical adenocarcinomas (27.8%), and four cases of mixed type squamous and glandular carcinomas (6.5%). We retrospectively reviewed these cases and six cases with clear cell morphology were identified. Four were classified as pure adenocarcinomas and two as mixed cell carcinomas with squamous and glandular elements. The clinicopathological features were re-assessed and additional information was obtained from the files of the 2nd Department of Obstetrics and Gynecology of our hospital. Nuclear and histological grading was performed on each neoplasm based on tumour architecture and the guidelines of Christopherson *et al*. [11] . Histochemististry (PAS, PAS-diastase, mucicarmine) and

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Table 1. — *Classification of cervical glandular carcinomas and related tumours (WHO - Pathology and Genetics of Breast and Tumours of the Female Genital System, IARC Press, Lyon 2003).*

| |
|---|
| Pure adenocarcinomas |
| Typical endocervical type |
| Variant |
| Well-differentiated villoglandular adenocarcinomas |
| Mucinous |
| Adenoma malignum (minimal deviation adenocarcinoma) |
| Intestinal type (including signet-ring cell and colloid adenocarcinoma) |
| Endometrioid |
| Variant |
| Minimal deviation adenocarcinoma |
| Clear cell |
| Serous |
| Mesonephric |
| Adenosquamous carcinoma |
| Glassy cell carcinoma |
| Adenoid basal carcinoma |
| Adenoid cystic carcinoma |
| Adenocarcinoma and neuroendocrine tumours |
| Carcinoma mixed (specify subtypes) |
| Metastatic adenocarcinoma |

immunohistochemistry for study of vimentin (V9 clone, ThermoScientific), cytokeratin 8/18 (K8.8+DC10, ThermoScientific), CEA (COL-1 clone, Neomarkers Fremont, CA), HMFG1 (1.10F3 clone), ER (6F.11, Novocastra), PgR (SP2, Neomarkers) were additionally performed in cases not studied previously. Moreover, we performed a mini-review on the field by using a Medline search for relative articles with the key word the term clear cell cervical carcinoma.

*Clinical and pathological findings*

One patient was a 32-year-old woman with a history of in utero DES exposure and HPV infection of the vulva. All the other patients were postmenopausal, aged 54-65 years old. A review of their records failed to reveal any history of in utero DES exposure. Abnormal vaginal bleeding was the presenting symptom in all patients. Pretreatment cytologic examination was positive for squamous cell carcinoma in two cases, suspicious for adenocarcinoma in two cases, and inconclusive in two cases.

All patients underwent radical hysterectomy, with the exception of the younger patient where the right ovary was preserved and translocated out of the pelvis to avoid menopausal symptoms.

In all cases the cervical tumours grossly presented as exophytic polypoid masses varying in size from 1.2-3 cm, occupying the transformation zone and extending to the endocervical canal. There was extensive infiltration of the cervical wall, but not extension to the pericervical tissues, the uterine cavity, the adnexa or the lymph nodes (Figures 1 and 2).

Microscopically, all tumours presented similar morphology consisting of tubules, cysts and solid sheets of large cells with clear cytoplasm and rather small cubical nuclei (Figure 3). Intracellular periodic acid-Schiff positive and diastase digestible material (glycogen) were also present in varying amounts. Mitotic figures were rare. In two cases, a synchronous development of an infiltrating squamous cell carcinoma was observed.

No hobnail cells, mesonephric remnants or cervical endometriosis were identified in our cases. Immunohistochemistry showed that the tumour cells were positive for CEA, cytokeratin and HMFG1 focally and negative for vimentin, ER and PgR.

The characteristic pathology and the immunophenotype estaplished the diagnosis of clear cell adenocarcinomas. All the tumours were classified as FIGO Stage I and histological grade 2. The follow-up of our patients ranged from six months to four years. In four of the older patients recurrence was observed during the study period. However, no death from the disease was reported during the follow-up period.

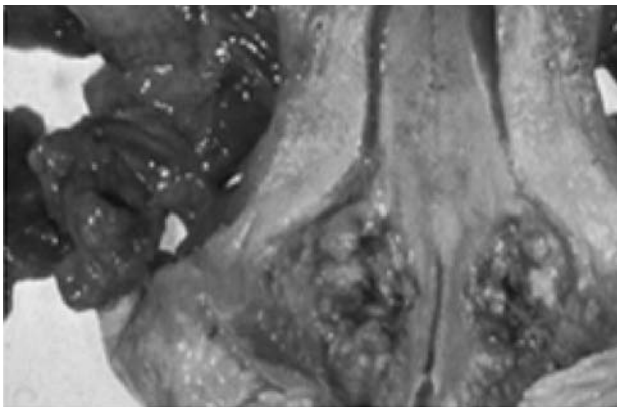

Figure 1. — Gross section of a uterus showing a large ulcerated endocervical tumour.

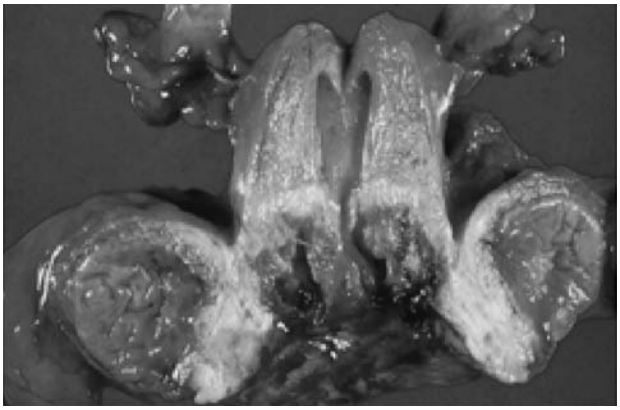

Figure 2. — Gross section of a radical hysterectomy specimen showing a fungating endocervical tumour.

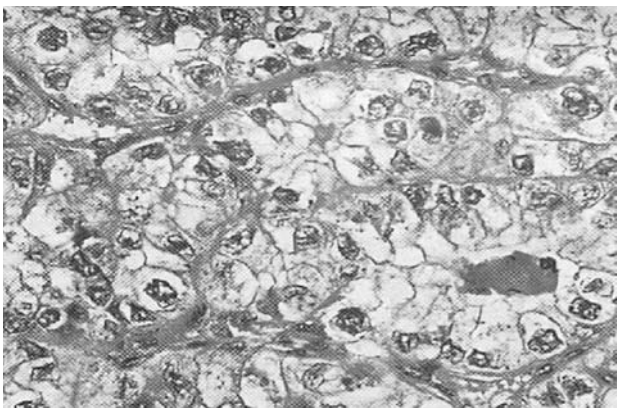

Figure 3. — Histological section of a cervical adenocarcinoma showing clear cell morphology and tubular pattern (haematoxylin-eosin x 250).

## Discussion

CCA was first observed in young women exposed to diethylstilbestrol (DES) in utero and a registry for clear cell tumours of the genital tract in young females was established reporting the main characteristics of this tumour in 1974 [5].

The age distribution of CCA is characteristic and has a bimodal peak, one around 20 years of age and the other in the 5th-6th decade of life [6]. In older patients primary CCA is rare and the pathogenesis is obscure. Some cases are associated with DES exposure while in most no such association is reported and endometriosis is implicated in the pathogenesis of the tumor [7, 8]. The most common complaint is vaginal bleeding, and on examination a polypoid, exophytic, or fungating cervical tumour is visible [10]. About two-thirds of the reported cases are FIGO Stage IB and the remaining Stage II or higher [10]. Depth of stromal invasion, FIGO stage, and pelvic nodal status are key prognostic indicators [10].

The microscopic patterns of clear cell adenocarcinoma are solid, tubulocystic, and papillary [12-14]. This growth pattern is important prognostically. A most favourable outcome is associated with a tubulocystic pattern, followed by papillary and solid patterns [12-14]. The cells comprising the tumour have abundant clear cytoplasm due to the accumulation of glycogen, as proven by histochemistry [12-14]. It should be emphasised that the clear cell morphology is caused by dissolution of intracellular proteoglucans due to histological preparations of the tissues, and is observed in many human neoplasms such as adenocarcinomas of the female genital system, neoplasms of the lungs and the kidney [15-17]. In our study, no histological or immunohistochemical differences between the six tumors were observed.

The differential diagnosis of this cervical tumour must be made from benign and malignant lesions such as florid microglandular hyperplasia, mesonephric hyperplasia and mesonephric tumours, Arias-Stella change and metastatic tumors with clear cell morphology (from uterus, ovaries or kidney) [15-18]. The difficulty in the differential diagnosis underlines the problems in the correct classification of CCA [4, 5, 7-9]. Histological features most helpful in the distinction from benign lesions include lack of a grossly visible mass, absence of a desmoplastic stromal reaction, lack of an infiltrative pattern, absence of cytologic atypia, low nuclear-cytoplasmic ratio, and lack of mitotic activity [10]. Clinical data and history are helpful in the differential diagnosis of CCA from metastatic tumours with clear cells while the immunophenotype of CCA, the presence of glucogen and the absence of mucin distinguish CCA from other primary cervical adenocarcinomas [10]. Atypical tuboendometrial glands of the cervix is a common co-finding of such carcinomas and for this reason, strong evidence exists that atypical cervical ectropion of the tuboendometrial type are precursors of clear cell adenocarcinoma [19, 20]. The histologic grading of CCA has proven difficult. However, in a previous study including 23 cases, the grading of neoplasms did not correlate with survival [9].

The proposed therapeutic approach is similar to the common infiltrating cervical carcinomas, with special consideration of fertility-preserving techniques for young patients [10, 21]. In the majority of the reported series, when the lesions were smaller than 2 cm and well differentiated, the prognosis was excellent and there were no deaths from the tumour [10].

In conclusion, CCA of the cervix is a distinct tumour that must be diagnosed and classified correctly in order to be properly and timely treated.

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