2018

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Mary G. Dandulakis
Washington University School of Medicine in St. Louis
Aidas J. Mattis
Washington University School of Medicine in St. Louis
Andrea R. Hagemann
Washington University School of Medicine in St. Louis
Ian S. Hagemann
Washington University School of Medicine in St. Louis

Gynecologic Oncology Reports 23 (2018) 16–19

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Cervical clear cell adenocarcinoma with an exceptionally low proliferation index: Report of a case

Mary G. Dandulakis[a], Aidas J. Mattis[a], Andrea R. Hagemann[b], Ian S. Hagemann[a,b,*]

[a] Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, MO, United States
[b] Department of Obstetrics & Gynecology, Washington University School of Medicine, St. Louis, MO, United States

ARTICLE INFO

Keywords:
Cervical cancer
Clear cell adenocarcinoma
Proliferation index
Precancerous conditions
Pathology

1. Background

Cervical clear cell adenocarcinoma (CCCA) is a rare malignancy constituting approximately 4% of cervical adenocarcinomas. It has historically occurred in the ectocervix of young women (teens to twenties) with in utero exposure to diethylstilbestrol (DES), a medication used to prevent pregnancy complications until 1971 (Loureiro and Oliva, 2014). Non-DES CCCA is associated with a bimodal distribution, arising in both the ecto- and endocervix of women in their 20s and 70s (Yang et al., 2017). It does not appear to be an HPV-driven malignancy, with the only clear risk factors being adenosis and endometriosis of the cervix as well as cervical tubo-endometrioid metaplasia (Loureiro and Oliva, 2014).

CCCA is a highly malignant cancer characterized by a high Ki-67 proliferation index and a prognosis similar to stage-matched squamous cell cervical cancer (Ju et al., 2017). With a 91% survival rate at 3 years for stage I CCCA and a rapid decline in survival to 22% at 3 years if advanced stage, CCCA is associated with late recurrence within gynecologic organs as well as distant metastasis including to the peritoneum and lungs (Thomas et al., 2008; Jones et al., 1993). CCCA can be confused with several benign mimics including microglandular hyperplasia, mesonephric hyperplasia and lobular endocervical glandular hyperplasia amongst others (Loureiro and Oliva, 2014).

While most of the mimics of CCCA, including mesonephric adenocarcinoma and gastric-type endocervical adenocarcinoma, have an associated non-malignant counterpart, to date there has been no benign counterpart ascribed to CCCA (Loureiro and Oliva, 2014) (Mikami and McCluggage, 2013).

We report on a woman who presented with atypical glandular cells on Pap screening and was ultimately diagnosed with CCCA after undergoing a biopsy and two cervical conization procedures. Findings on her initial surgical specimen showed an extremely low-grade tumor, illustrating the diagnostic difficulty of CCCA, and possibly representing a benign counterpart or precursor.

2. Case

Written consent was provided and is available upon request. A 41-year-old woman (gravida 1, para 1) with abnormal uterine bleeding was found to have atypical glandular cells on Pap test, with negative HPV co-testing and a benign endometrial biopsy. A transvaginal ultrasound revealed a simple ovarian cyst with otherwise normal uterus and adnexa. Subsequent colposcopy with biopsy was interpreted as an atypical glandular proliferation, with a note that the findings could be concerning for clear cell carcinoma.

Due to lack of a definitive diagnosis, she proceeded to a loop electrosurgical excision procedure (LEEP). The LEEP biopsy displayed a tubulocystic proliferation involving all margins. The architecture of the proliferation was a mixture of simple-appearing glands of variable size (Fig. 1A). The simple glands were lined by a single layer of inconspicuous cells, lacking nuclear atypia and without apparent eosinophilic or clear cytoplasmic inclusions; the glands contained strongly eosinophilic secretions (Fig. 1B). Some cells lining the glands had more prominent nuclei and an increased nuclear-to-cytoplasmic ratio (Fig. 1C). No nucleoli were apparent. There was focal evidence of hobnailing. A few areas showed intracystic papillary structures lined by

* Corresponding author at: Campus Box 8118, 425 S. Euclid Ave., St. Louis, MO 63110, United States.
E-mail address: hagemani@wustl.edu (I.S. Hagemann).

https://doi.org/10.1016/j.gore.2017.12.006
Received 9 November 2017; Received in revised form 29 December 2017; Accepted 30 December 2017
Available online 02 January 2018

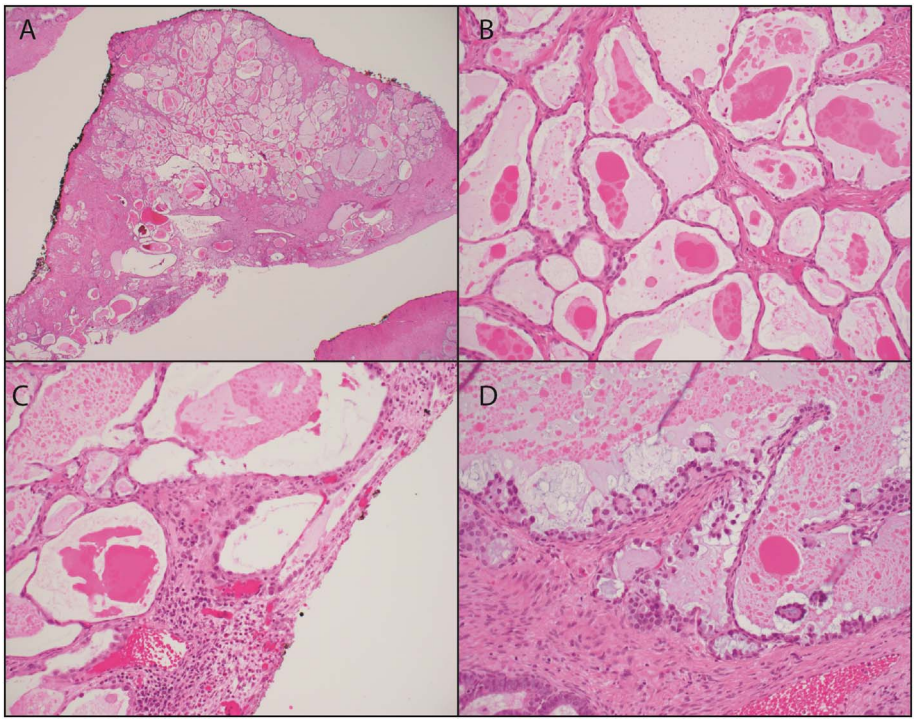

Fig. 1. (A) Low-power photomicrograph of clear cell lesion in LEEP specimen (original magnification 20 ×). (B) Low-power photomicrograph illustrating cysts lined by bland, flattened cells, with eosinophilic luminal secretions (100 ×). (C) Rare cells with higher nuclear-to-cytoplasmic ratio and atypical nuclear features (200 ×). (D) Intracystic papillary projections (200 ×).

atypical cells, with hyalinized stromal cores (Fig. 1D). No eosinophilic or clear cytoplasmic inclusions were visible and very few mitotic figures were present.

Due to the overall benign appearance of the lesion, microglandular hyperplasia, lobular endocervical glandular hyperplasia and mesonephric hyperplasia were considered as possible diagnoses. The focal presence of papillary structures with hobnailing and atypical nuclei, however, raised concern for clear cell carcinoma.

Immunostains were performed (Fig. 2 and Table 1). Stains for estrogen (Fig. 2A) and progesterone receptors were negative, essentially ruling out a diagnosis of microglandular hyperplasia, which the literature suggests is either concomitantly estrogen and progesterone receptor-positive (ER + /PR +) or ER + /PR–. Staining for TTF-1 (McFarland et al., 2016) and GATA-3 (Roma et al., 2015), two stains often positive in mesonephric lesions, was negative. The specimen was weakly androgen receptor-positive, which is typical of cervical tissue, but tends to be lost in mesonephric adenocarcinoma (Silver et al., 2001; Wani et al., 2008). Notably the biopsy was p16-negative, essentially ruling out an HPV-associated malignancy. p53 (Fig. 2B) showed a wild-type pattern with occasional positive cells, not diffusely positive as is

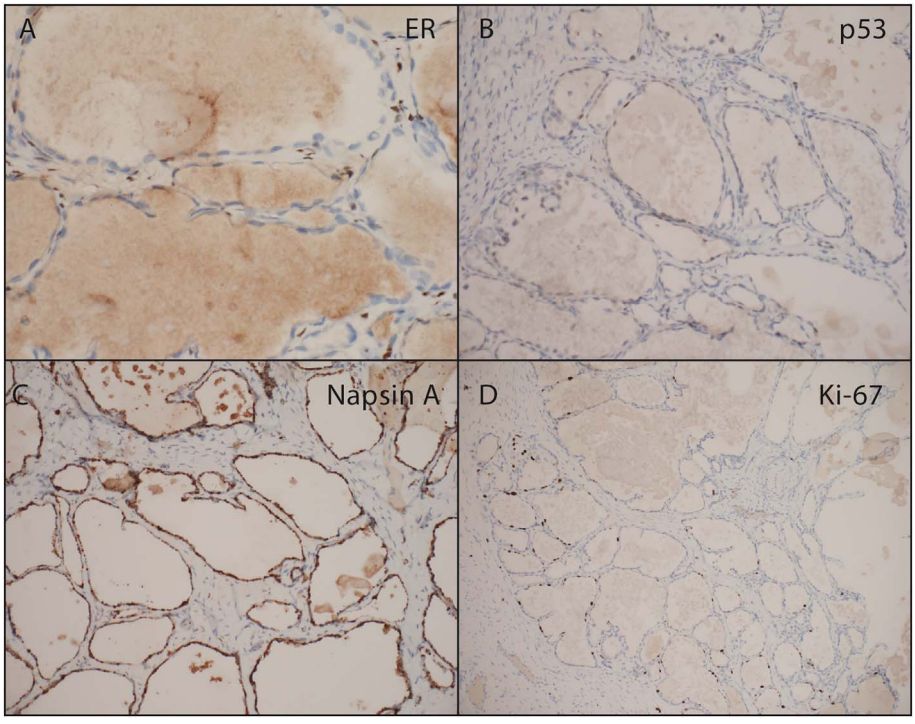

Fig. 2. Representative immunostains performed on the LEEP specimen. (A) ER (original magnification 400 ×). (B) p53 (200 ×). (C) Napsin A (200 ×). (D) Ki-67 (100 ×).

Table 1
Immunohistochemical profile of the lesion and of diagnoses in the differential.

	Microglandular hyperplasia	Usual-type endocervical adenocarcinoma	Mesonephric hyperplasia or carcinoma	Clear cell carcinoma	Case
ER	+ (Qiu and Mittal, 2003)	– (Loureiro and Oliva, 2014)	– (Silver et al., 2001)	– (Ju et al., 2017; Loureiro and Oliva, 2014)	–
PR	+ or – (Qiu and Mittal, 2003)	– (Loureiro and Oliva, 2014)	– (Silver et al., 2001)	– (Ju et al., 2017; Loureiro and Oliva, 2014)	–
AR	NR	NR	+ in 33% (Silver et al., 2001)	NR	Weak +
TTF-1	NR	– (Siami et al., 2007)	+ (McFarland et al., 2016)	NR	–
GATA-3	NR	– (Roma et al., 2015)	+ (Roma et al., 2015)	NR	–
Bcl-2	– (Loureiro and Oliva, 2014)	– (Pavlakis et al., 2010), + in 27% (McCluggage et al., 1997)	+ (Pavlakis et al., 2010)	+ (Waggoner et al., 1998)	+
Napsin A	NR	NR	NR	+ (Ju et al., 2017)	+
p16	– (Stewart and Crook, 2015)	+ (Pavlakis et al., 2010)	– (Pavlakis et al., 2010)	+ in 75% (Ueno et al., 2013)	–
p53	WT (Loureiro and Oliva, 2014)	+ (McCluggage et al., 1997)	WT (Loureiro and Oliva, 2014)	Usually WT (Ju et al., 2017; Loureiro and Oliva, 2014)	WT
Ki-67	Low, < 5% (Qiu and Mittal, 2003)	High, > 10% (Pavlakis et al., 2010)	MH: low, 1–2% (Loureiro and Oliva, 2014) MC: high, 5–36% (Loureiro and Oliva, 2014)	High, 34% ± 11% (Ju et al., 2017)	Low (< 1%)

NR, not reported; WT, wild-type; mut, mutant.

typically associated with clear cell adenocarcinoma (Loureiro and Oliva, 2014). Napsin A (Fig. 2C), typically positive in gynecologic clear cell adenocarcinoma, and Bcl-2, positive in either clear cell adenocarcinoma or mesonephric lesions, were both positive. Ki-67 (Fig. 2D) indicated a low proliferation index of < 1%, which is atypical in rapidly growing lesions and not consistent with any histotype of adenocarcinoma (Pavlakis et al., 2010). Ki-67-positive cells were present only at the periphery of the lesion, while the center of the lesion was negative.

While the histologic and immunohistochemical findings (particularly clear Napsin A positivity) were concerning for clear cell adenocarcinoma, the low mitotic and proliferative activity and wild-type p53 staining were suggestive of a potentially less malignant lesion that might be captioned as clear cell hyperplasia (an entity not specifically described in the literature) or another glandular proliferation with clear cell phenotype. A diagnosis of "glandular proliferation with clear cell features" was rendered, with concern noted for CCCA. The margins of excision were extensively positive, and more definitive classification was felt to require examining the edges of the lesion.

A second cone excision was performed. This specimen showed similar findings with negative margins, and underlined the expansile, non-infiltrative nature of the process, with rare smaller, infiltrative glands at the perimeter. Given the size of the lesion (7 mm in width and 5 mm in depth in the largest specimen), and the lack of any other suitable nosologic category, a diagnosis of CCCA was felt to best describe the process, but note was made of the unusual features.

In the absence of literature to support treatment of CCCA with only cone excision, minimally invasive radical hysterectomy was performed and showed no residual tumor. No adjuvant treatment was pursued. The patient developed a postoperative deep vein thrombus (DVT) and was placed on enoxaparin for 6 months. Follow-up was otherwise uneventful at 3 months. No further follow-up data were available due to the short time elapsed.

3. Discussion

We report on the histology from a woman with abnormal uterine bleeding, who was found to have atypical glandular cells of unknown significance on Pap. Subsequent surgical specimens, while concerning for cervical clear cell adenocarcinoma by morphology and immunoprofile, appear to show a process with low malignant potential. Of some interest, the patient experienced a postoperative DVT, which is common in patients with clear cell carcinoma. Due to the low proliferation index (Ki-67 < 1%), uneventful oncologic follow-up is anticipated, although only a short follow-up interval has elapsed at present. The distribution of proliferating cells only at the periphery of the lesion is a phenomenon we have not previously observed and that has not been extensively discussed in the literature. It may imply that the lesion has a propensity for maturation or self-limitation.

Cervical clear cell carcinoma comprises approximately 4% of all cervical adenocarcinomas, affecting early reproductive age women as well as post-menopausal women. Non-DES related CCCA has a prognosis similar to that of cervical squamous cell carcinoma as well as other cervical adenocarcinomas. Due to its rarity and therefore lack of evidence to specifically guide treatment, it is currently treated similarly to cervical squamous cell carcinoma (Thomas et al., 2008). There are no systematic reports of treatment less than hysterectomy.

Cervical squamous cell carcinoma has a well-known precursor lesion, as do many types of adenocarcinoma, such as cervical adenocarcinoma NOS (adenocarcinoma in situ), mesonephric adenocarcinoma (mesonephric hyperplasia) and gastric type endocervical adenocarcinoma (lobular endocervical glandular hyperplasia) (Mikami and McCluggage, 2013; Zaino, 2000). To date, no premalignant analogue of cervical clear cell adenocarcinoma has been described. We propose that the pathology in this patient may be indicative of a benign or premalignant analogue (i.e., a forme fruste) of cervical clear cell

adenocarcinoma. Further studies are mandatory before such an entity (putatively best classified as clear cell hyperplasia) can be defined.

Financial disclosures

None.

Acknowledgements

The authors thank Drs. Jennifer Sehn, Hannah Krigman and Horacio Maluf for helpful discussions.

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