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Case report

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

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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

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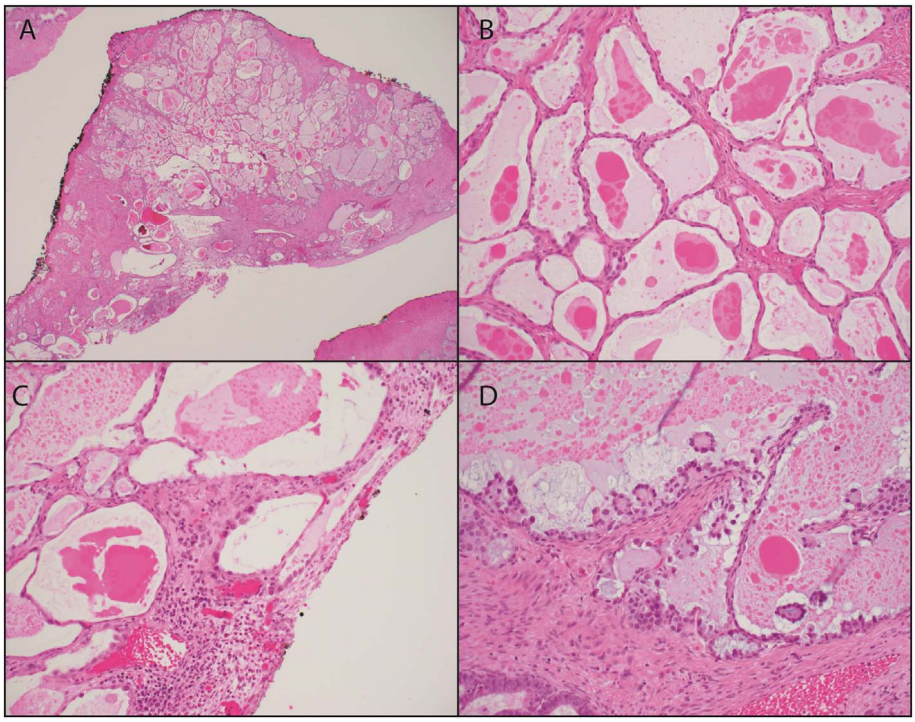

Fig. 1. (A) Low-power photomicrograph of clear cell lesion in LEEP specimen (original magnification 20 ×). (B) Low-power photomicrograph illustrating cysts lined by bland, flattened cells, with eosinophilic luminal secretions (100 ×). (C) Rare cells with higher nuclear-to-cytoplasmic ratio and atypical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

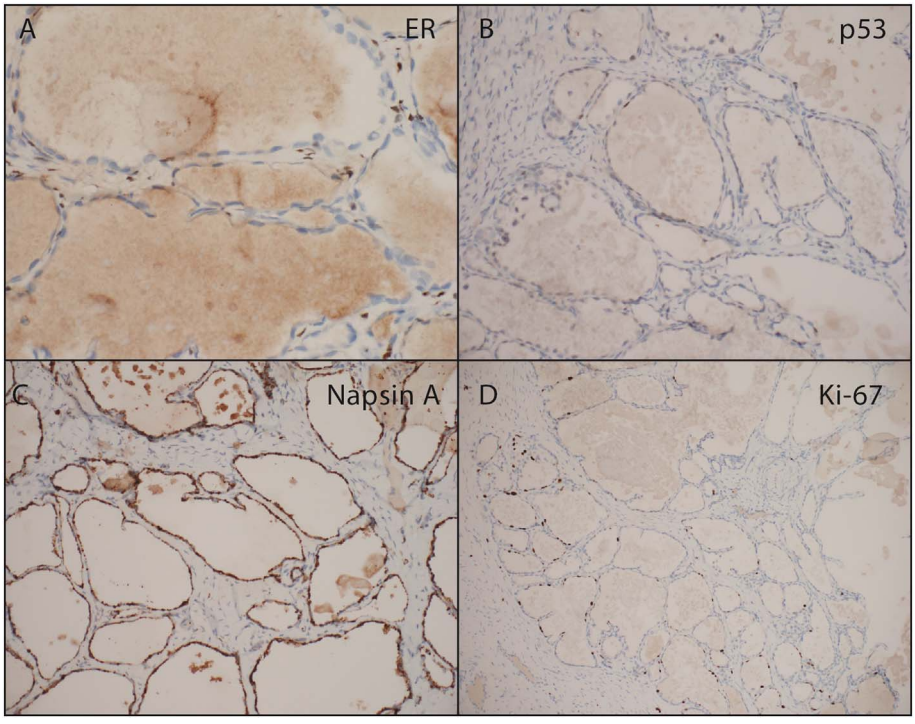

Fig. 2. Representative immunostains performed on the LEEP specimen. (A) ER (original magnification 400 ×). (B) p53 (200 ×). (C) Napsin A (200 ×). (D) Ki-67 (100 ×).