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Case series

Ciliated/tubal-type in-situ and invasive endocervical adenocarcinoma: Report of three cases with limited follow-up and review of the literature

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ABSTRACT

In situ (AIS) and invasive endocervical adenocarcinoma have two broad categories, HPV-associated (HPV) and HPV-independent groups. (1) These entities show various types of cell morphology. Tubal and tubo-endometrioid type metaplasia of the cervix is a benign finding (Suh and Silverberg, 1990). Tubal metaplasia is also encountered in benign and malignant endometrial lesions. During cervical biopsy interpretations, differentiating the site of origin of the tissue is often tricky. We intend to document three cases of the sparsely reported hrHPV-associated ciliated/tubal-type endocervical AIS and invasive adenocarcinoma and bring it to the attention of readers how to avoid any misinterpretation during routine sign-out. Only three of fifty-three cases of hrHPV-associated AIS and invasive adenocarcinoma were of ciliated/tubal type in our department over a 5-year time. The presence of tubal-type epithelium should not automatically trigger the assumption of endometrial origin of the lesion. These cases are red herrings as tubal/ciliated type dysplasia, and carcinoma is rare and have potential to escape accurate diagnosis.

1. Background

In situ and endocervical adenocarcinoma are divided into HPV-associated and HPV-independent groups by the World Health Organization (WHO) (WHO classification of tumors editorial board: Female genital tumors, 2020). If partially treated or untreated, endocervical adenocarcinoma in situ often progresses into invasive carcinoma. An accurate diagnosis at an early stage is crucial to avoid morbidity and mortality. The ciliated/tubal type AIS is one of the cytomorphological variants of HPV-associated neoplasms. Benign tubal metaplasia of the cervix and endometrium is a differential diagnosis of tubal type endocervical AIS and is a potential pitfall. (Brown and Wells, 1986). Both tubal metaplasia and ciliated type AIS show fallopian tube-type epithelial differentiation. However, if associated with cytologic atypia and brisk mitosis, the presence of cilia may not be disregarded as a hyperplastic/reactive process. Additional evaluation, including ancillary testing, p16, and ki67, is recommended to establish the diagnosis (WHO classification of tumors editorial board: Female genital tumors, 2020). Estrogen and progesterone receptors are helpful; characteristically, the benign mimics tend to be positive for the latter immunohistochemical stains (WHO classification of tumors editorial board: Female genital tumors, 2020).

2. Case reports

2.1. Case 1

A 38-year-old women with a history of atypical squamous cells cannot rule out high grade (ASC-H) on a Pap smear in 2016. The high-risk HPV (hrHPV) DNA test in 2016 was positive, and she underwent an endocervical curetting.

The endocervical curettage (ECC) showed fragments of epithelium with atypical nuclei, a high nuclear to cytoplasmic ratio, and hyperchromatic nuclei; a diagnosis of ungraded dysplasia, favor high-grade was rendered, in addition to metaplastic squamous epithelium. Also present was tubo-endometrioid metaplasia with reactive changes. No ancillary testing was done. Because of the abnormal EEC finding, a colposcopic examination was done followed up by a cervical cold knife cone biopsy. Cervical cone biopsy revealed endocervical adenocarcinoma in situ (AIS) with positive endocervical margins (Fig. 1). Both proximal, distal, and radial (deep) margins were negative for in situ lesions. An uncommon finding was noted in the cone biopsy where benign tubal-type epithelium transitioned into tubal/ciliated type endocervical adenocarcinoma in situ. The epithelial cytomorphology in the in situ lesion had identical ciliary/tubal features as was seen in the

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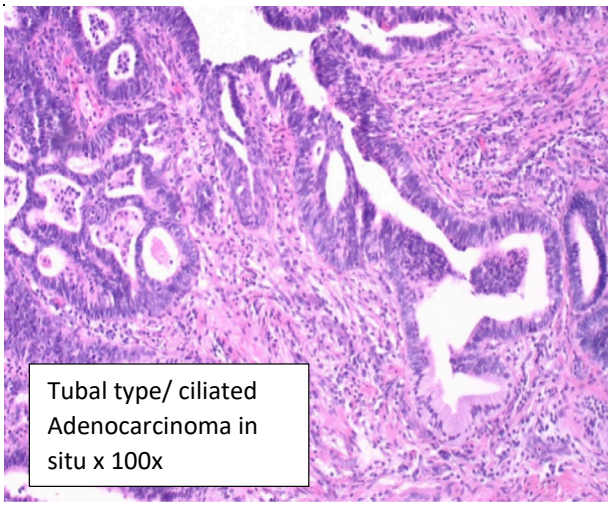

Fig. 1. Tubal type/ ciliated adenocarcinoma in situ × 100x.

benign tubal metaplastic epithelia, except for marked nuclear atypia with hyperchromasia, high N: C ratio, and increased mitosis (Fig. 2); the diagnosis was supported by high proliferative index (Ki67) and block p16 positivity and negative Progesterone receptor (Figs. 3-4). The patient was offered hysterectomy as standard of care. However, the patient refused hysterectomy because of her desire to preserve fertility. As an alternative she is under surveillance for the last 56 months with routine Pap smears, HRHPV testing and endocervical curetting which are all negative. She is continuously monitored with Pap smears and HRHPV testing and are negative for both. The last follow up was in June 2021.

2.2. Case 2

In a more recent case, the second patient is a 33-year-old referred to our hospital from a local community hospital after a recent hysterectomy for further management. She had a negative Pap with a high-risk HPV 16 positive. Initially, a cervical biopsy revealed the endocervical AIS, tubal/ciliated type. Based on the biopsy finding at the outside facility, she underwent a simple hysterectomy there, skipping the cone biopsy, which would have been the standard of care. Standard care in this situation would have been a radical hysterectomy.

A review of the consultation material confirmed the diagnosis of hrHPV-associated AIS and adenocarcinoma. The hysterectomy slides showed HPV-associated endocervical adenocarcinoma and AIS. The exciting feature of the invasive and AIS components was the presence of

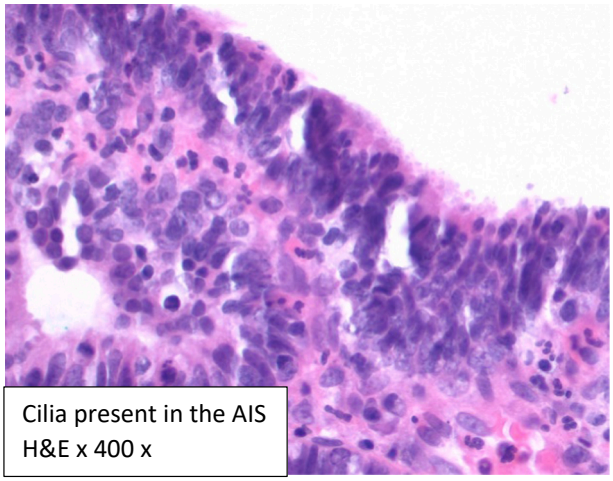

Fig. 2. Cilia present in the AIS H&E × 400 x.

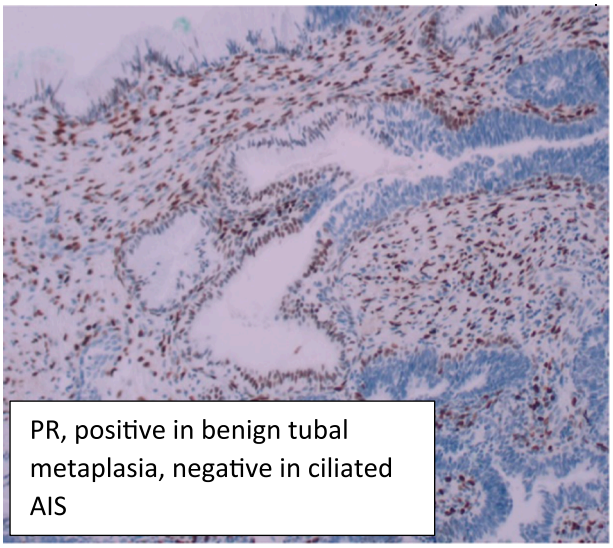

Fig. 3. PR, positive in benign tubal metaplasia, negative in ciliated AIS.

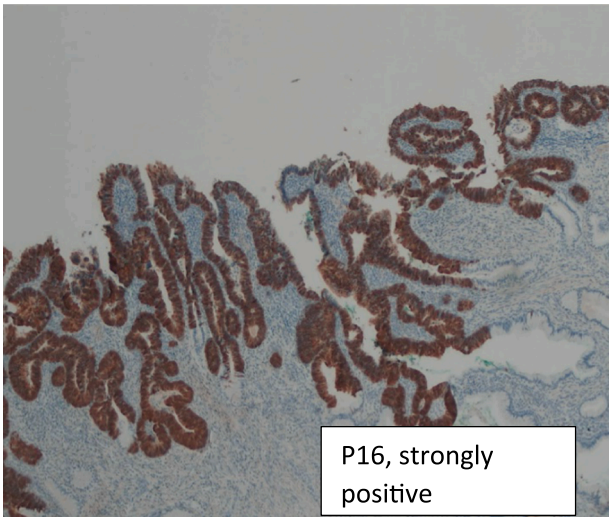

Fig. 4. P16, strongly positive.

tubal/ciliated type cells. It was a well-differentiated, 9 mm invasive tumor with a five mm depth of invasion (pT1a2Nx) (FIGO 1A2). The surgical margins were negative, and no lymph vascular space invasion was identified.

At this institution, completion staging procedure with laparoscopic lymph node dissection, oophorectomy, and parametrectomy was offered but he patient opted lymph node dissection and oophorectomy and declined parametrectomy.

Patient received HRT immediately post-operative period and has tolerated it well. Based on the negative metastatic workup, further treatment was not warranted.

2.3. Case 3

The third case represents a 35-year-old woman initially presented with atypical squamous cells of unknown significance (ASCUS) and positive HPV 16 in April 2019. Her endocervical curettage, performed in May of the same year, showed adenocarcinoma in situ (AIS). Moreover, the cervical biopsy confirmed AIS. She underwent a cold knife cone biopsy afterward in the same year. The cone biopsy showed endocervical glands with benign tubal metaplasia and AIS. The dysplastic

epithelial cells of AIS had cilia. All surgical margins of resection were negative. Ancillary immuno-histochemical staining revealed block positive p16 expression and negative PR staining, but the surrounding benign tubal metaplasia showed positive for PR. Patient opted for surveillance to preserve fertility. The follow-up Pap and the ECCs so far have been negative, except an ASCUS in May 2020. Her HPV status has also been negative from 10/10/2019 to current. She has been disease-free for almost three years.

3. Discussion

Freidel et al. first described endocervical adenocarcinoma in 1953. AIS was an incidental finding, as the patient received treatment for squamous cell carcinoma in situ (Friedell and McKay, 1953). The changes seen in AIS are often subtle and require careful attention (Boon et al., 1981; Buscema and Woodruff, 1984; Qizilbash, 1975; Ostör et al., 1984; Van Roon et al., 1983). Various cytomorphologic patterns and the etiology of AIS are described in the literature, including the sparsely identified ciliary/tubal type. However, considered a benign finding it is seen more frequently in endometrial lesions, both benign and malignant forms, especially in patients with a history of abnormal uterine bleeding. The cilia are also present in the ciliated/tubal type of AIS/carcinoma and benign tubo-endometrioid metaplasia in the cervix The ciliated/tubal AIS is an hrHPV associated lesion and may arise in a background of tubal and tubo-endometrioid metaplasia. The presence of marked cytologic atypia, increased mitosis, high proliferation index (ki67), and the absence of estrogen/progesterone receptors (ER/PR) staining by immunohistochemistry help differentiate the ciliated AIS from other benign mimics. ER and PR staining are observed in 20–27% of primary cervical adenocarcinomas. However, some studies have found down-regulation of ER/PR expression in HPV-related cervical dysplasia (Fujiwara et al., 1997; Bekkers et al., 2005). Furthermore, we have encountered only three out of 54 cases of this variant of endocervical adenocarcinoma over five years at our institution, indicating its rarity. In an endocervical curettage specimen, fragmented atypical endocervical mucosa with AIS may be confused with an endometrial lesion. Immunohistochemical staining patterns of p16 and HPV-ISH (HPV In Situ Hybridization) offer additional support for the endocervical origin. In our first case, the endocervical curettage did not show distinct cilia. However, a cervical cone biopsy, which offered more tissue to examine, had glands with benign tubal differentiation transitioning into tubal type endocervical adenocarcinoma in situ. Marked cytologic atypia in ciliated AIS should differentiate this lesion from benign tubal metaplasia. So, attention to detail is the key in recognizing these entities: brisk mitosis and high Ki67 by immunohistochemistry are also helpful findings. In the second case: according to the World Health Organization (WHO) book on tumors, high-risk HPV-associated invasive endocervical adenocarcinoma has three patterns: non-destructive invasion, early/focally destructive invasion, and diffusely destructive invasion (WHO classification of tumors editorial board: Female genital tumors, 2020; Zaino, 2002). The 3rd case reported in this series is an example of pattern-A with well-demarcated glands, rounded counters, absent solid growth pattern, lymphovascular invasion, and desmoplasia. This case had distinct tubal differentiation and cilia in the invasive component. However, the WHO does not explicitly describe the ciliated/tubal type of invasive adenocarcinoma and its prognosis; apparently, such cases exist. In the third patient's sample there was significant cytological atypia in the epithelial cells in the curettage to warrant a diagnosis of AIS. Her cone biopsy showed tubal metaplasia and ciliated type AIS. All the cases described here are young women, a typical scenario of HPV-associated endocervical adenocarcinoma (Stolnicu et al., 2018; Hodgson et al., 2019).

The first patient has been disease-free for 56 months, the third for almost 36, and the second patient is relatively recent— being node-negative on surgical staging should predict a favorable prognosis. However, the data is limited because not many cases are available in English literature most prominent being Schlesinger describing endocervical adenocarcinoma of tubal type in 1999 (Schlesinger and Silverberg, 1999). Also, the presence of cilia is not documented in relevant cases consistently. Another helpful finding noted to differentiate this entity is the presence of peg/non-ciliated cells commonly seen in tubal type epithelium (Suh and Silverberg, 1990). The reader would agree on the essence of identifying and documenting ciliated/tubal type AIS with follow-up of this relatively rare variant of hrHPV-associated endocervical adenocarcinoma to elucidate any significance of these findings better. A significant number of well-documented cases will unveil the true biological significance of this lesion in the coming future.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

The patient signed a consent form that allows the use of the material for educational purposes without disclosing the unique identifiers of the patient.

CRediT authorship contribution statement

Shivali Marketkar: Writing, visualization, **Joyce Ou:** Resources, Supervision. **C. James Sung:** Supervision. **M. Ruhul Quddus:** Conceptualization, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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