

# A case of non-HPV related primary endometrioid adenocarcinoma of the cervix

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## ARTICLE INFO

### Keywords:

Cervical adenocarcinoma  
Non-HPV associated  
Primary endometrioid  
IECC guidelines  
Endocervical carcinoma

## ABSTRACT

**Objective:** Primary endometrioid adenocarcinoma of the cervix is a rare subtype of adenocarcinoma that has often been misclassified in the literature due to the lack of clear-cut diagnostic criteria. A new classification system has recently been developed that aims to provide clarity and reproducibility when diagnosing subtypes of endocervical adenocarcinoma. This case report demonstrates the difficulty in diagnosing primary endometrioid adenocarcinoma, application of the new diagnostic guidelines, and a review of the literature of this rare non-HPV subtype.

**Case:** A 76 year-old women presented with postmenopausal bleeding and was found to have an exophytic cervical mass. Biopsies showed an adenocarcinoma of probable endometrial origin. She underwent a robotic-assisted simple hysterectomy with bilateral pelvic lymph node sampling and omental biopsy. Final pathology report demonstrated a primary endometrioid adenocarcinoma of the cervix, measuring 2.4 cm in size, diagnosed using the recently developed International Endocervical Adenocarcinoma Criteria and Classification (IECC) system. Patient was then treated with external beam radiation therapy and concurrent chemotherapy, followed by vaginal brachytherapy. She had no evidence of disease at her 15-month follow-up visit.

**Conclusion:** Primary endometrioid adenocarcinoma of the cervix is a rare and diagnostically challenging tumor of the cervix. This case illustrates the challenges associated with diagnosis of this endocervical carcinoma subtype and the need for a multi-disciplinary approach when determining treatment.

## 1. Introduction

The incidence of invasive endocervical adenocarcinoma (ECA) and its variants has increased over the past few decades, accounting for about 25% of cervical malignancies. This is in contrast to the more prevalent invasive squamous cell carcinoma (SCC), whose incidence has dramatically decreased in most developed countries due to the implementation of national screening and vaccination programs. SCC is almost always human papillomavirus (HPV) related with the most prevalent serotypes as HPV 18, 16, and 45. Although ECAs are commonly associated with HPV, 10–15% are non-HPV related (Stolnicu et al., 2019).

ECA often presents with vaginal bleeding at a mean age of about 50 years of age (Kurman, 2014). On clinical exam, an exophytic mass or ulcerated lesion maybe noted. Morphologically, ECAs are a heterogeneous group with several distinct histological tumor types.

Traditionally, ECA have been classified according to the World Health Organization (WHO) system (Kurman, 2014). This system has been recently challenged by experts as it often difficult to apply in daily practice, lacks reproducibility, and lacks clinical significance. The WHO classification also makes an assumption that all ECAs are HPV related. To correct these failures, a panel of international experts developed the International Endocervical Adenocarcinoma Criteria and Classification (IECC). The IECC classification divides ECAs into two categories: HPV-associated (HPVA) and non-HPV-associated (NHPVA). NHPVA are then subcategorized into five morphologically distinct groups: endometrioid, gastric-type, serous, clear cell, mesonephric, and NOS (Stolnicu et al., 2019; Stolnicu, 2018; Stolnicu, 2018) (Fig. 1).

Based upon the IECC classification, endometrioid-type ECA is a rare variant of ECA with an overall prevalence of 1.1% (Stolnicu, 2018). This is in contrast to the WHO classification system which reports the prevalence of primary endometrioid adenocarcinoma between 7% and

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<https://doi.org/10.1016/j.gore.2020.100579>

Received 24 March 2020; Received in revised form 24 April 2020; Accepted 27 April 2020

Available online 01 May 2020

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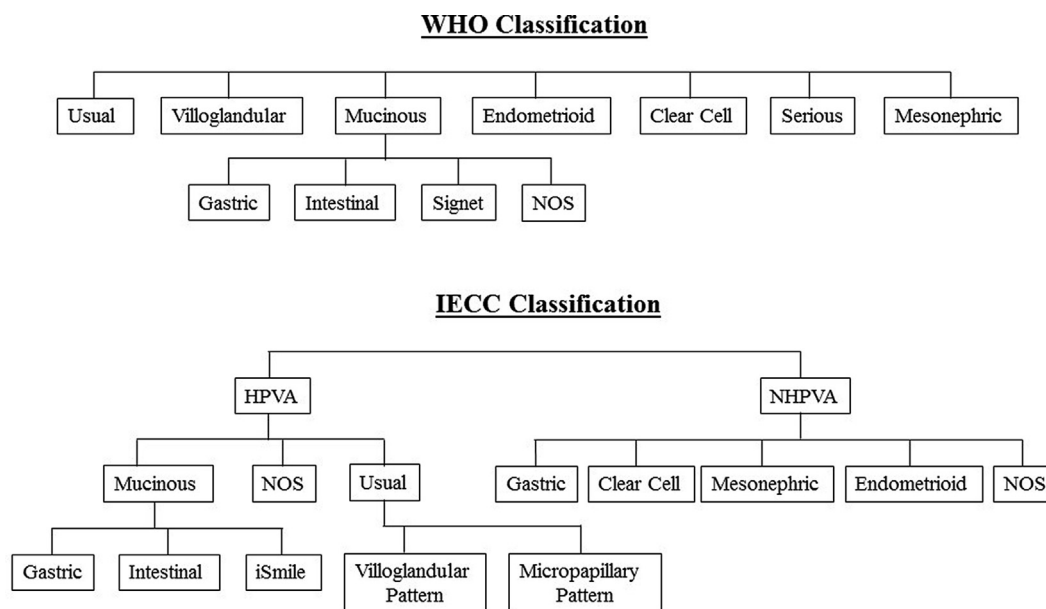


Fig. 1. Endocervical adenocarcinoma classification systems. (Kurman, 2014; Stolnicu, 2018).

50%. This discrepancy is based largely on the reclassification of endometrioid-type ECA to usual-type ECA using the more stringent IECC classification (Stolnicu et al., 2019). We present a case herein of a rare endometrioid-type ECA that was diagnosed using the criteria proposed by IECC classification.

## 2. Case

A 76 year old nulliparous female was referred to gynecology oncology for postmenopausal bleeding and an abnormal pap smear that indicated HPV negative highly atypical epithelial cells, cannot determine glandular or squamous. Patient was noted on transvaginal ultrasound to have a uterus measuring  $5 \times 2.7 \times 2.6$  cm, with diffusely heterogeneous endometrium raising possibility of a polyp despite the normal thickness (3 mm.) History was significant for an ovarian tumor at age 20, status-post exploratory laparotomy and bilateral salpingo-oophorectomy. Patient was unable to provide information about histological type or stage but stated that she had not received adjuvant treatment. Patient was diagnosed at age 73 with breast cancer, status-post lumpectomy with no chemotherapy/radiation treatment indicated, and was being treated with tamoxifen. Family history was significant for her mother and maternal aunt with breast cancer, and maternal aunt with ovarian cancer. She had not undergone any genetic testing.

Patient was noted on physical exam to have an irregular polypoid 2–3 cm mass, inseparable from the cervix in the vaginal vault. Parametria and rectovaginal septum were palpably smooth. Biopsy of the mass revealed adenocarcinoma of probable endometrial origin, favoring high grade, as supported by ER positive, PR and p16 negative immunohistochemical staining (IHC). Further characterization upon definitive resection was needed.

CT chest, abdomen, and pelvis was obtained and showed no evidence of disease outside of the uterus. Patient underwent a robotic-assisted simple hysterectomy with bilateral pelvic lymph node sampling and omental biopsy. There was no gross evidence of extrauterine disease at time of surgery. Microscopically, the tumor showed an admixture of growth patterns, including glandular, papillary and micropapillary, with destructive stromal invasion (Fig. 2). Tumor cells showed scant to moderate amount of eosinophilic to focally clear cytoplasm with intermediate nuclear grade and lack of mucin (Fig. 3). The tumor did not extend to the lower uterine segment and endometrium was unremarkable. IHC was significant for a wild-type P53 pattern with

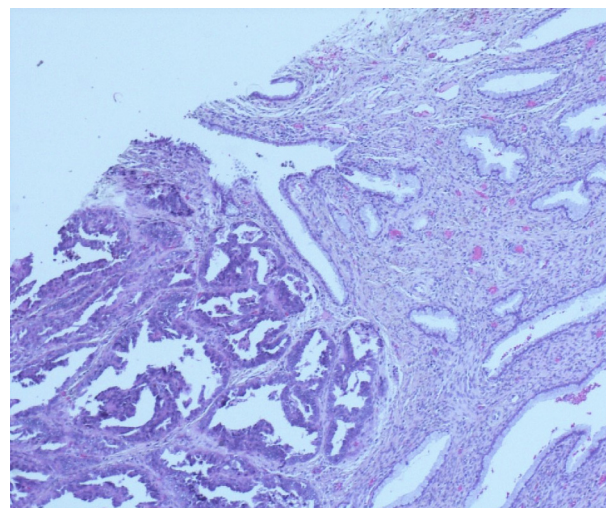


Fig. 2. Tumor infiltrating normal endocervical mucosa (4×, low power magnification, H&E).

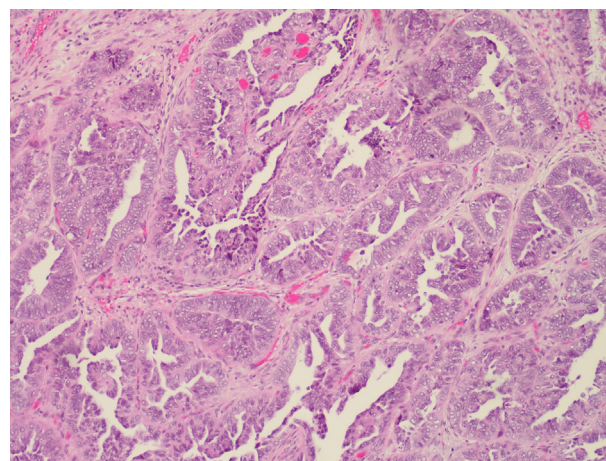


Fig. 3. Tumor with glandular architecture and tumor cells exhibiting scant eosinophilic cytoplasm and lack of mucin (20×, H&E).

positive staining for ER and CEA. Tumor cells were also focally positive for P16 and TTF-1, negative for GATA3 and HR-HPV RNA. There was a retained expression for PTEN, ARID1A, and DNA mismatch repair proteins (MLH1, PMS2, MSH6, MSH2). Final pathology revealed a 2.4 cm tumor, invading at least 12 mm cervical stroma, focal tumor present at cauterized circumferential margin, suspicious LVSI, negative vaginal margin and lymph nodes. Based on these findings a final diagnosis of stage IB1 non-HPV endometrioid-type ECA was rendered. After discussion with a multi-disciplinary tumor board, the decision was made for external beam radiation therapy and chemotherapy with cisplatin 40 mg/m<sup>2</sup> weekly for 6 weeks followed by vaginal brachytherapy for five treatments. The patient did well after surgery and tolerated chemoradiation without incident. Follow-up exam and PET CT with no evidence of disease at her 15 month post-surgery.

### 3. Discussion

Primary endometrioid adenocarcinoma is defined by the WHO as an ECA arising in the cervix that has endometrioid morphologic features, such as tumor cells that are lacking mucin and have a scant, deeply eosinophilic cytoplasm resembling endometrial-type epithelium. Although widely used, many experts believe that this diagnostic criteria is nonspecific and has led to discrepancies in reporting with incidence of primary endometrioid adenocarcinoma ranging from 7% to more than 50% (Stolnicu et al., 2019). In 2018, the IECC classification was published by Stolnicu et al. in order to provide clarity in diagnosing ECA subtypes by linking morphological features to etiology (HPV status) (Stolnicu, 2018). Using the IECC classification, endometrioid-type ECA is defined as endometrioid morphology with “confirmatory endometrioid features,” and lacking HPV features, such as apical mitoses and karyorrhexis. These “confirmatory endometrioid features” include at least focally identified low-grade endometrioid glands lined by columnar cells, with pseudostratified nuclei demonstrating no more than moderate atypia, with or without squamous differentiation, and/or endometriosis present (Stolnicu, 2018; Lim, 2016). Using the WHO classification system, Stolnicu et al demonstrated that 41% of the 371 cases analyzed in their study would have been classified as endometrioid-type. However, using the IECC classification, the majority of those cases would be reclassified as usual-type ECAs, leaving only 3 cases of endometrioid-type ECA (Stolnicu, 2018). The authors concluded that this reclassification is more in line with the etiology of endometrioid-type ECAs as they are believed to arise from existing cervical endometriosis (Stolnicu, 2018; Hirschowitz et al., 2007).

As a result of the lack of specific diagnostic criteria for endometrioid-type ECA, demographic and clinical parameters is difficult to determine. Recently, Stolnicu et al. published clinical outcomes for a group of 187 cases diagnosed using the IECC classification and had at least a 5-year follow-up. The authors found that NHPVAs are generally larger tumors, diagnosed at FIGO Stage II or more advanced in > 50% of cases, and occur in older patients as compared to HPVAs tumors. NHPVAs were also more frequently associated with lymphovascular invasion, lymph node metastasis, and local and distant recurrence. Of note, the predominant ECA in the NHPVAs cohort was gastric-type with only two cases of endometrioid-like ECA used in the analysis (Stolnicu et al., 2019; Stolnicu, 2019).

The National Comprehensive Cancer Network (NCCN) treatment guidelines for cervical cancer does not differentiate treatment based upon histological type. Treatment of early invasive adenocarcinoma (IB1-IIA) typically consists of surgery (radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection) or radiotherapy, which is usually administered with concurrent cisplatin-based chemotherapy (Koh, 2019). Studies have shown an increased effectiveness of surgery compared to radiotherapy (without chemotherapy) in patients with adenocarcinoma. It has been postulated that this could be the result of the increased effectiveness of the surgery or a radioresistance of adenocarcinoma. Thus, experts agree that chemotherapy

should be considered when radiotherapy is administered (Koh, 2019; Baalbergen et al., 2013).

Prognosis of endometrioid-type ECA is unknown due to the rarity of the disease. In general, the 5-year survival rate for women with invasive cervical cancer is 92%. The major prognostic factors affecting survival include age, nodal status, tumor volume, and depth of invasion. Although controversial, another prognostic factor is histologic type. A study of 24,562 patients with cervical cancer demonstrated that among women with early stage disease, patients with adenocarcinoma were 39% more likely to die compared to those with squamous cell carcinoma (Galic, 2012). An additional independent prognostic factor may be HPV status of the tumor. Univariate analysis of the 187 cases published by Stolnicu et al. demonstrated significant difference in the 5-year survival between HPV-positive and HPV-negative adenocarcinomas that had received surgery and adjuvant treatment, with radiotherapy alone or in combination chemotherapy. The authors also found that patients with HPV-positive adenocarcinoma with pelvic recurrence had a better overall survival, disease free survival, and progression free survival when compared to patients with NHPVA (Stolnicu, 2019). However, further studies are needed to clarify the effect of HPV status on prognosis.

Post-treatment surveillance of patients with cervical cancers, including endometrioid-type ECA, consists of history and examination every 3–6 months for 2 years, 6–12 months for 3–5 years, and then annually based on patient’s risk of disease recurrence. Cervical/vaginal cytology can be done annually. However, the likelihood of detecting an asymptomatic recurrence by cytology alone is low. Experts recommend that imaging and laboratory assessment should be reserved for those individuals that present with symptoms or examination that is suspicious for disease recurrence (Koh, 2019).

In conclusion, we presented a rare case of endometrioid-type ECA that was diagnosed using the IECC classification system. This case provides further supporting evidence of the strength of the IECC classification system as it classifies ECAs based upon HPV status. This case also illustrates the challenges associated with diagnosis of this endocervical tumor subtype and the need for a multi-disciplinary approach when determining treatment.

### CRedit authorship contribution statement

**Kieran Seay:** Visualization, Writing - original draft. **Bethany Bustamante:** Conceptualization, Writing - review & editing. **Seema Khutti:** Resources, Writing - review & editing. **Marina Frimer:** Project administration, Supervision.

### Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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