Superficially Spreading Endocervical Adenocarcinoma *in situ* with Multifocal Microscopic Involvement of the Endometrial Surface: A Case Report with Emphasis on the Potential for Misdiagnosis Based on Endometrial Curettage Specimens

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**Abstract**

Misdiagnosis of endocervical adenocarcinoma (EAC) as endometrial endometrioid carcinoma (EEC) is one of the major concerns when evaluating endometrial curettage specimens. It is difficult to differentiate EAC involving the endometrium from EEC, particularly when the specimens have only a few small tumor fragments. We report a case of endocervical adenocarcinoma *in situ* (AIS) with multifocal microscopic involvement of the endometrium. The endometrial curettage specimen obtained from an 82-year-old woman consisted of a large volume of blood and fibrin, with small endometrial tissue fragments showing microscopic foci of atypical glandular proliferation. Based on the presence of complex glands with stratified mucin-poor columnar epithelium and intermediate-grade nuclear atypia, a preoperative diagnosis of grade 1 EEC was made. However, the hysterectomy specimen revealed an endocervical AIS involving the endocervix and low uterine segment. Frequent mitotic figures and apoptotic bodies, characteristic of AIS, were present. The endometrium showed a few microscopic foci of atypical glandular proliferation involving the surface only. Their histological features were similar to those of the endocervical AIS. Immunohistochemically, the atypical glands exhibited block p16 positivity. The final diagnosis was a superficially spreading endocervical AIS with multifocal microscopic involvement of the endometrial surface epithelium. In summary, small tumor tissues in an endometrial curettage may lead to misdiagnosis of AIS or EAC as...
EEC, especially when the pathologists are unaware of the possibility of microscopic endometrial involvement of AIS or EAC. The origin of the tumor can be correctly determined based on a combination of histological features and immunostaining. Endocervical AIS involving the endometrium should be included in the differential diagnosis of neoplastic glandular lesions in endometrial curettage specimens. An accurate diagnosis in these cases is important because of its significant implications for clinical management.

**Introduction**

The endometrial versus endocervical origin of small tumor fragments in the endometrial curettage is difficult to distinguish by their morphological features alone [1]. Most frequently, the tumor shows atypical glandular proliferation of stratified columnar mucin-poor epithelium with intermediate-grade nuclear atypia, making it difficult to differentiate between endometrial endometrioid carcinoma (EEC) and endocervical adenocarcinoma (EAC). In particular, specimens with large amounts of blood, and a few small tumor fragments present a diagnostic challenge.

Endocervical adenocarcinoma in situ (AIS) is a premalignant lesion that can lead to the usual-type EAC [2]. By definition, endocervical AIS normally involves only columnar epithelium and does not invade the cervical stroma [2, 3]. It exhibits a variable anatomical distribution, extending along the endocervical canal for several centimeters, sometimes involving the entire circumference of the cervix. Nevertheless, an extension of the endocervical AIS proximal to the internal orifice is uncommon and the involvement of the endometrium, fallopian tube, or ovary is even rarer. However, several studies have reported a subset of endocervical tumors with minimal to no evidence of stromal invasion manifesting as metastatic tumors of the upper female genital tract [4–6].

In this study, we describe the detailed histological features and immunophenotype of an endocervical AIS involving the endometrial surface and initially misdiagnosed as EEC on the endometrial curettage specimen. A comprehensive analysis of the multifocal endometrial involvement of endocervical AIS will serve to improve the understanding of this rare condition and help pathologists make a correct diagnosis.

**Case Presentation**

An 82-year-old woman presented with vaginal bleeding. She had no previous history of gynecological disease. Abdominopelvic magnetic resonance imaging and transvaginal ultrasonography revealed hematometra without a definite mass. The bilateral adnexa were atrophied. No lymph node enlargement, peritoneal seeding, or abdominal metastasis was identified. Diagnostic endometrial curettage was performed. Histologically, the curetted specimen showed a large amount of blood and fibrin, consistent with hematometra, as seen with imaging (Fig. 1A–B). Several small endometrial tissue fragments comprised approximately 10% of the total specimen volume. A few foci of atypical glandular proliferation showed complex architectural pattern and intermediate-grade nuclear atypia (Fig. 1C), including mild enlargement, moderate pleomorphism, and inconspicuous nucleoli (Fig. 1D). The cytoplasm was scant. Several endometrial strips were also observed (Fig. 1E), and they showed the same degree of nuclear atypia as seen in the atypical glands attached to the fibrotic stroma (Fig. 1F). There was a transition from normal endometrial glandular epithelium to stratified columnar epithelium of variable thickness resembling normal proliferative endometrial glands. Even
though the specimen appeared to consist mainly of blood at low-power magnification, a scant amount of atypical glands was observed at medium-to-high-power magnification. The diagnosis of grade 1 EEC was made. For the biopsy-proven but radiologically invisible endometrial carcinoma, the patient underwent total hysterectomy with bilateral salpingo-oophorectomy.

Grossly, no visible mass was identified in the endocervix and endometrial mucosa. The uterine serosa, parametrium, and bilateral adnexa were unremarkable. Histologically, the endocervix showed an AIS measuring 16 mm. On low-power magnification, AIS spread horizontally up to the low uterine segment (Fig. 2A–B). No stromal invasion was identified. Frequent mitotic figures and apoptotic bodies, characteristic of human papillomavirus (HPV)-related EAC, were present (Fig. 2C). The endometrium of the body and fundus showed a few separate microscopic foci of atypical glandular proliferation measuring <2 mm and involving the endometrial surface (Fig. 2D). Based on the nuclear stratification, intraluminal papillary projection, and abundant eosinophilic cytoplasm, the atypical glandular epithelium was clearly demarcated from the adjacent inactive endometrial surface epithelium (Fig. 2E). No
stromal invasion was noted. On high-power magnification, the nuclear morphology and the degree of atypia were similar to those in endocervical AIS (Fig. 2F). Mitotic figures and apoptotic bodies were detected, although not as frequent as observed in the endocervical AIS. Immunostaining revealed block p16 positivity in the atypical gland on the endometrial surface.
(Fig. 2G–H), whereas the adjacent endometrial glandular epithelium showed patchy p16 positivity (Fig. 2I). The final pathological diagnosis was superficially spreading endocervical AIS with microscopic multifocal involvement of the endometrial surface epithelium.

All available previous slides from the endometrial curettage specimen were reviewed. The foci of atypical glandular proliferation, initially misinterpreted as EEC, were morphologically identical to those of endocervical AIS. A few areas had mitotic figures and apoptotic bodies, although they were not readily identifiable. Immunostaining revealed that the atypical glands exhibited block p16 positivity, confirming the involvement of endocervical AIS (Fig. 3A–B). In contrast, immunostaining for estrogen receptor (ER) and progesterone receptor (PR) highlighted the endometrial glands and stroma only (Fig. 3C–D).

The patient did not receive further treatment. At the first postoperative outpatient visit, she was well without any evidence of disease recurrence. She was referred to another tertiary hospital to continue postoperative care closer to home.

**Discussion**

It is essential to distinguish the endometrial involvement in EAC versus EEC for appropriate pathological staging and clinical management. However, it is difficult to differentiate between the endometrial versus endocervical origin of small tumor fragments from the
curettage specimens by their morphological features alone. The distinction between EAC and EEC is still challenging due to the following [7]: First, both tumors have mucinous and endometrioid-like features. The EAC is most often characterized by a hybrid of mucinous and endometrioid-like features, usually with increased mitotic figures and apoptosis. Some of the EECs can also have varying degrees of mucinous differentiation. Second, both tumors most often exhibit entirely well-differentiated glandular proliferation and a villoglandular growth pattern. Third, when tumors involve both the endometrium and the endocervix, the interpretation of small tissue fragments from biopsy or curettage specimens is difficult. For example, an AIS or EAC extending into the endometrium simulates atypical hyperplasia/endometrioid intraepithelial neoplasia or endometrioid carcinoma, and EEC involving the endocervix closely resembles EAC. The diagnosis of superficially spreading AIS with multifocal microscopic endometrial involvement requires careful histological examination of the uterine body and cervix to exclude the possibility of EEC.

Nevertheless, the following histological features help distinguish EAC from EEC: a higher degree of nuclear atypia, markedly increased mitotic activity, frequent apoptotic bodies, and the absence of squamous morules [7, 8]. Compared with EEC, the EAC is more likely to exhibit a higher degree of nuclear atypia, including moderate-to-severe pleomorphism and hyperchromasia, often with numerous apically situated mitotic figures and basally situated apoptotic bodies. Atypical mitotic figures are also frequently seen in EAC but are very rare in low-grade EEC. The foci of squamous differentiation (squamous morules) are more frequently found in EEC but absent in EAC.

In routine practice, immunostaining with a few selected markers can also readily distinguish between EECs and EACs. The most useful marker is p16, followed by ER and PR [1]. p16 immunoreactivity is a surrogate marker for high-risk HPV infection [9]. HPV-associated EAC almost always shows block positivity for p16, compared to the variable and non-diffuse positivity seen in low-grade EEC. While most EECs express ER and PR, most EACs exhibit focal and weak ER expression and a loss of PR expression.

In summary, EAC can be misdiagnosed as EEC when evaluating small tumor tissues in the endometrial curettage, particularly when the pathologists are unaware of the possibility of microscopic endometrial involvement of EAC. In most cases of a suspected endometrial lesion, their origin can be correctly determined based on a combination of histological features and immunostaining results, even when the former is based upon the examination of relatively small samples. The presence of frequent mitotic figures and apoptotic bodies indicate endocervical AIS since endometrial low-grade endometrioid carcinoma generally do not have the notable mitotic activity and apoptotic bodies. Accurate diagnosis in these cases is very important because it has significant implications on pathological staging, management, and prognosis.

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Statement of Ethics

Written informed consent for publication was obtained from the patient. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (Seoul, Republic of Korea) (2020-07-116).
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Inwoo Hwang: conceptualization, data collection, data analysis, and manuscript drafting; Jiyeon Lee: data collection and manuscript editing; Kyue Hee Choi: data analysis and manuscript editing; Jiheun Han: manuscript editing; Hyun-Soo Kim: conceptualization, data analysis, manuscript drafting, manuscript editing, funding acquisition, and supervision. All authors read and approved the final manuscript.

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