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Original article

ProExC is a novel marker for distinguishing between primary endometrial and endocervical adenocarcinomas

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KEYWORDS

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Abstract *Background:* Distinguishing endocervical adenocarcinoma (ECA) from endometrial adenocarcinoma (EMA) is clinically significant and cannot always be made on the basis of morphology alone or clinical findings.
The aim of this study was to study the potential utility of ProExC as a new marker for cervical adenocarcinoma, and to evaluate a panel of monoclonal antibodies composed of p16, ER, PR, and vimentin, and assess their diagnostic value in distinguishing between ECA and EMA.
Methods: Immunohistochemistry using monoclonal antibodies to ProExC, p16, estrogen receptor (ER), progesterone receptor (PR), and vimentin, was performed to examine 30 cases, including 10 ECAs and 20 EMAs.
Results: Eight out of 10 cases (80%) of ECA were positive for ProExC, whereas only 2 cases of EMA (10%) were positive. The difference of ProExC expression in the two groups of malignancy was statistically significant ($p = 0.003$). P16 was positive in 8 cases (80%) of ECAs and in 4 cases (20%) of EMAs. Estrogen receptor was negative in all cases of ECA, while it was positive in 95% of EMA. Progesterone receptor was positive in 2 cases (20%) of ECA and in 16 cases (80%) of EMA. Vimentin was positive in only one case (10%) of ECA, and in 16 cases (80%) of EMA.
Conclusion: ProExC is a novel immunohistochemical marker for differentiating ECA from EMA and its inclusion in a panel of immunohistochemical markers including p16, ER, PR, and vimentin is recommended when there is morphological and clinical doubt as to the primary site of endocervical or endometrial origin.

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Introduction

In Egypt, current estimates indicate that every year, 514 women are diagnosed with cervical cancer and 299 die from the disease. Cervical cancer ranks as the 14th most frequent cancer among women in Egypt, and the 12th most frequent cancer

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among women between 15 and 44 years of age [1]. About 10.3% of women in the general population are estimated to harbor cervical HPV infection at a given time. Human papillomavirus (HPV) infection contributes to nearly most of the cases of cervical cancer based on the observed presence of HPV DNA within these cancers [2] and more than half of the HPV-associated cervical cancers are attributed to infection with HPV16 [2–4].

Morphologic distinction of endocervical adenocarcinoma from its endometrial counterpart is clinically significant due to their differences in management and prognosis [5]. The treatment of endometrial carcinoma begins with surgical staging and intraoperative assessment of the grade and extent of tumor in the uterus while primary endocervical carcinoma is managed by an initial radical hysterectomy and pelvic lymphadenectomy with or without adjuvant radiotherapy [5–7].

The differential diagnosis between the two gynecologic neoplasms can be problematic especially when the tumor involves the lower uterine segment or upper endocervix [5]. Histologic features that favor endocervical origin include eosinophilic fibrotic stroma, apical mitotic figures, basal apoptotic bodies, presence of adenocarcinoma in situ or squamous dysplasia, and monomorphous appearance. Features that favor endometrial origin include the presence of endometrial stromal or foam cells, complex endometrial hyperplasia, and polymorphous appearance [8].

Before the identification of HPV as a probable etiologic agent in the development of endocervical adenocarcinomas and the advent of commercially available markers for detecting HPV, most of the immunohistochemical markers used; such as estrogen and progesterone receptors and vimentin, targeted endometrial adenocarcinomas. Carcinoembryonic antigen (CEA) was the only positive marker for endocervical adenocarcinomas. However, the use of CEA is significantly limited by the high degree of variability in results depending on the methodology and antibody used [9].

Recent studies have investigated the role of HPV in endocervical adenocarcinomas by using HPV ISH or p16 to identify the presence of high-risk HPV. The p16INK4a (cyclin-dependent kinase inhibitor 4) is a tumor suppressor protein that binds to cyclin–cdk4/6 complexes, which blocks kinase activity and inhibits progression to the S phase of the cell cycle in the nucleus. Over-expression of p16 has been observed in high-grade CINs and carcinomas and, therefore, has been used as a surrogate marker and a useful addition to the panel for the differential diagnosis between endocervical and endometrial primaries [2,3,10–14]. Similar to p16, ProExC has been recently proposed as an additional marker for HPV related cancer cervix. Recent studies have demonstrated that ProExC targets cell cycle proteins, minichromosome maintenance protein-2 (MCM2), and topoisomerase II-a (TOP2A) [15,16]. MCM2 is a member of the DNA licensing factor family and a cell proliferation marker. TOP2A is an enzyme that unknots DNA for DNA replication, transcription, chromosome segregation, and cell cycle progression. Both MCM2 and TOP2A have been shown to be over-expressed when viral DNA integrates into the host genome leading to increased levels of E6 and E7 and aberrant S-phase induction [8,17–23].

High-risk human papillomaviruses (HPV) encode two oncogenes, E6 and E7 and their integration into the host DNA causes their increased expression and the development of cervical cancers [19–24].

The E6 protein consists of 158 amino acid residues and contains two zinc-finger binding motifs. The E6 protein stimulates cell proliferation by promoting degradation of the tumor suppressor p53. Such E6-stimulated degradation interferes with biological functions of p53; thus disrupting the control of cell cycle progression, leading finally to increased tumor cell growth [25].

E7 is a multifunctional protein known for its ability to inactivate the tumor suppressor pRb. E7 binds to more than 20 cellular proteins [24]. The most well characterized target of E7 is the retinoblastoma tumor suppressor, Rb [24,25].

E7 binds to a region of the Rb protein called the 'pocket domains'. The 'pocket domain' sequences of Rb are essential for its tumor suppressor function. One of the major biochemical functions of Rb is to bind E2F-family transcription factors and inhibit the expressions of replication enzyme genes. E7 disrupts the interaction between Rb and E2F, resulting in the release of E2F factors in their transcriptionally active forms. Furthermore, E7 modulates E2F activity by other mechanisms; E7 also inhibits the cyclin-dependent kinase (cdk) inhibitors p21 and p27, and may directly activate both cyclin A/cdk2 and E2F1 [25].

Various studies in the literature have investigated the expression of ProExC in different tissues and organs. For example, Chen et al. described that ProExC is a useful proliferation marker for high-grade VIN [26].

While Bhandarkar et al. reported that ProExC stains positive in recurrent respiratory papilloma (RRP) and the authors suggested that further studies are necessary to determine whether ProExC can be used in the triage of cases of clinically aggressive RRP for closer follow-up or frequent operative intervention [27].

Similarly, Sánchez-Hernández et al. found that ProExC was observed in the whole epidermis thickness in 86.5% of Bowen's disease [28].

Walts et al. observed positive staining for ProExC in Paget cells in all of the 26 cases of Paget's disease irrespective of the tissue site (extramammary, mammary) and in melanoma cells in all of the 12 cases of primary perineal melanoma [29].

Materials and methods

Formalin-fixed, paraffin-embedded tissue blocks containing adenocarcinomas of endocervix and endometrium were obtained retrospectively from the archives of the Department of Pathology, Faculty of Medicine, Tanta University during the period between 2005 and 2010. Only primary endocervical and endometrial adenocarcinomas from hysterectomy or conization specimens with negative hysteroscopy were included in this work. Small biopsy specimens were excluded from the study.

The study group consisted of 20 cases of EMA and 10 cases ECA. The endometrial adenocarcinoma cases were classified as follows: 16 cases were endometrioid adenocarcinoma and 4 cases were serous adenocarcinoma. On the other hand, the ECA included: 8 endocervical mucinous adenocarcinoma and 2 cases of endocervical endometrioid adenocarcinoma.

Immunohistochemical analysis was done with the following commercially available antibodies: ProExC, p16, ER, PR, and vimentin. The characteristics of antibodies used for evaluation were summarized in Table 1.