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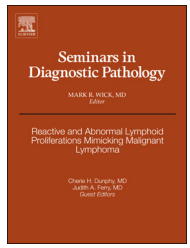

# Updates in diagnostic immunohistochemistry in endometrial carcinoma

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ABSTRACT

Diagnostic difficulty in the morphologic assessment of endometrial carcinomas may arise in pathology practice. Challenges in tumor classification exist especially in the setting of high-grade carcinomas. These include FIGO grade 3 endometrioid, serous, clear cell, and undifferentiated carcinomas, in addition to carcinomas of mixed cell type and those exhibiting ambiguous morphologic features. This comprehensive review details key morphologic and immunophenotypic features of prototypic endometrial carcinomas, including a description of both well-established and novel immunohistochemical markers in the evaluation of these tumors. It also provides recommendations regarding prudent use of these ancillary techniques in distinguishing between various histologic subtypes of endometrial carcinoma that frequently result in persistent diagnostic problems.



## Introduction

Established morphologic criteria usually allow for the correct diagnosis of most endometrial carcinomas. However, diagnostic challenges may arise particularly in the setting of high-grade endometrial carcinomas, which include FIGO grade 3 endometrioid, serous, clear cell, and undifferentiated carcinomas, as well as mixed epithelial and morphologically ambiguous carcinomas. Substantial problems in the diagnostic reproducibility of high-grade endometrial carcinomas exist even among experienced gynecologic pathologists.[1] Furthermore, recent integrated genomic, transciptomic, and proteomic analyses of endometrial carcinomas from The Cancer Genome Atlas have shown that a quarter of FIGO grade 3 and a smaller group of low-grade endometrioid carcinomas harbor somatic copy number alterations and mutations characteristic of serous carcinoma, suggesting discordant genotype and morphology in a significant proportion of endometrial carcinomas.[2] In a smaller study, lack of genotypic and histologic correlation was observed in approximately 30% of high-grade endometrial carcinomas.[3]

While morphology currently remains the gold standard in the evaluation of endometrial cancers, immunohistochemistry can serve as a helpful adjunct in improving genotypic and histologic concordance and aiding diagnosis in difficult cases. This review focuses on recognized and novel immunohistochemical features of prototypical endometrial carcinomas and provides recommendations for applying immunohistochemical techniques to major problems in their differential diagnosis with an emphasis on high-grade cancers. The distinction between primary endometrial carcinomas and involvement of the endometrium by extrauterine primaries of gynecologic or non-gynecologic origin is not discussed here. Details regarding hereditary non-polyposis colorectal cancer- or Lynch syndrome-related endometrial carcinomas are beyond the scope of this review, but may be found elsewhere in this issue.

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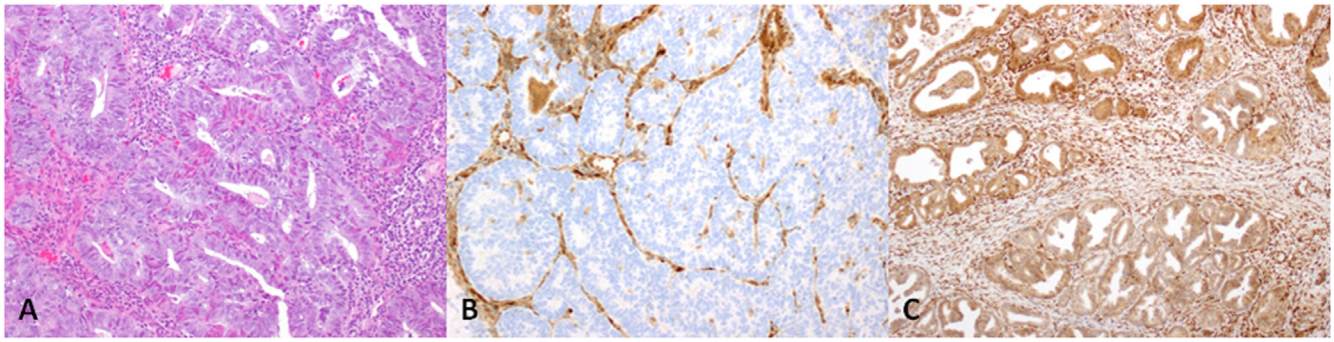


**Fig. 1 – PTEN expression patterns. (A) Endometrioid carcinoma, FIGO grade 1 demonstrating complete loss of PTEN staining with positive internal control (B). (C) Serous carcinoma with retained PTEN expression (H&E not pictured).**

## Immunophenotype of prototypic histotypes

### *Endometrioid carcinoma*

Endometrioid carcinomas express pan-cytokeratins, EMA, CA125, Ber-EP4, B72.3, CK7, and vimentin, and usually lack CK20 expression.[4,5] Cytoplasmic CEA expression is rare, but when present, it is limited to the apical membranes of tumor cells.[6–8] Endometrioid carcinomas with mucinous differentiation may show increased CEA expression as well as CDX2 staining.[9,10]

Virtually all FIGO grade 1 and grade 2 and approximately half of FIGO grade 3 endometrioid carcinomas express ER and PR.[6,11–16] A minority of FIGO grade 2 and grade 3 endometrioid carcinomas also demonstrate p53 overexpression (strong staining in >75% of tumor nuclei), although most endometrioid carcinomas show a wild-type pattern with only focal and patchy staining in <50% of tumor nuclei.[11,16–23] Nuclear and cytoplasmic beta-catenin expression secondary to *CTNNB1* mutation has been found in approximately one-third of low-grade endometrioid carcinomas, especially those with squamous differentiation.[11,24–26] p16 expression is typically limited to scattered tumor cells, but may appear more widespread in the occasional FIGO grade 3 endometrioid carcinoma; however, the presence of diffuse and strong p16 expression characteristic of serous carcinoma is typically lacking in FIGO grade 3 endometrioid carcinomas.[19,27]

Mutations in *PTEN* and less commonly, promoter hypermethylation, have been found in large proportion of endometrioid carcinomas, resulting in a loss of expression in up to 75% of these tumors.[11,28–33] However, interpretation of PTEN immunoexpression is often challenging. The use of the 6H2.1 antibody appears to surpass others in detecting the loss of expression which is defined by the absence of expression in >90% of tumor cells with an intact positive internal control (cytoplasmic and occasionally nuclear staining of endometrial stroma and non-neoplastic endometrial glandular epithelium) (Fig. 1).[34,35]

Abnormal expression of DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) is seen in approximately one-third of endometrioid carcinomas (Fig. 2).[36–38] This finding usually results from MLH1 promoter hypermethylation in sporadic tumors, but may be secondary to mutations in any DNA mismatch repair gene in the setting of hereditary nonpolyposis colorectal carcinoma or Lynch syndrome. Aberrant protein expression is defined by loss of nuclear staining in tumor cells. Weak or focal nuclear staining of tumor cells in an otherwise morphologically homogeneous tumor is interpreted as retained protein expression. Correct interpretation of DNA mismatch repair protein expression in the carcinoma requires a valid positive internal control (nuclear staining of non-neoplastic endometrial glands and stroma) and distinction from tumor-infiltrating lymphocytes. Loss of protein expression is usually seen in pairs (MLH1 coupled with PMS2 and MSH2 coupled with MSH6), but isolated loss of expression of MSH6 without MSH2 loss or isolated loss of PMS2 without MLH1 loss may be encountered (Fig. 2). While exceptions to this rule exist, repeat staining is recommended in such occasions for confirmation.

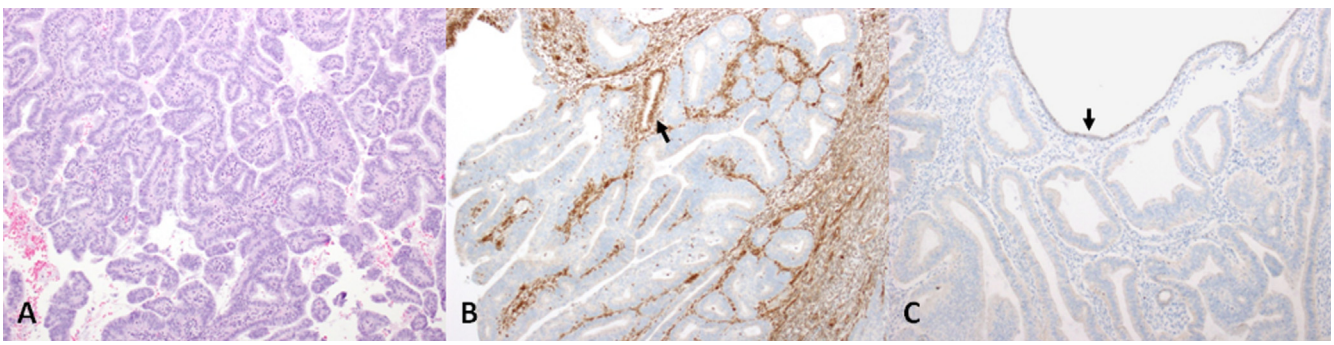


**Fig. 2 – (A) Endometrioid adenocarcinoma, FIGO grade 1 demonstrating (B) MSH2 and (C) MSH6 loss with positive internal control (arrows). MLH1 and PMS2 protein expression is retained (not pictured).**