PROPATH
THE FOCUS
Immunohistochemistry

Endocervical vs. Endometrial Adenocarcinoma:

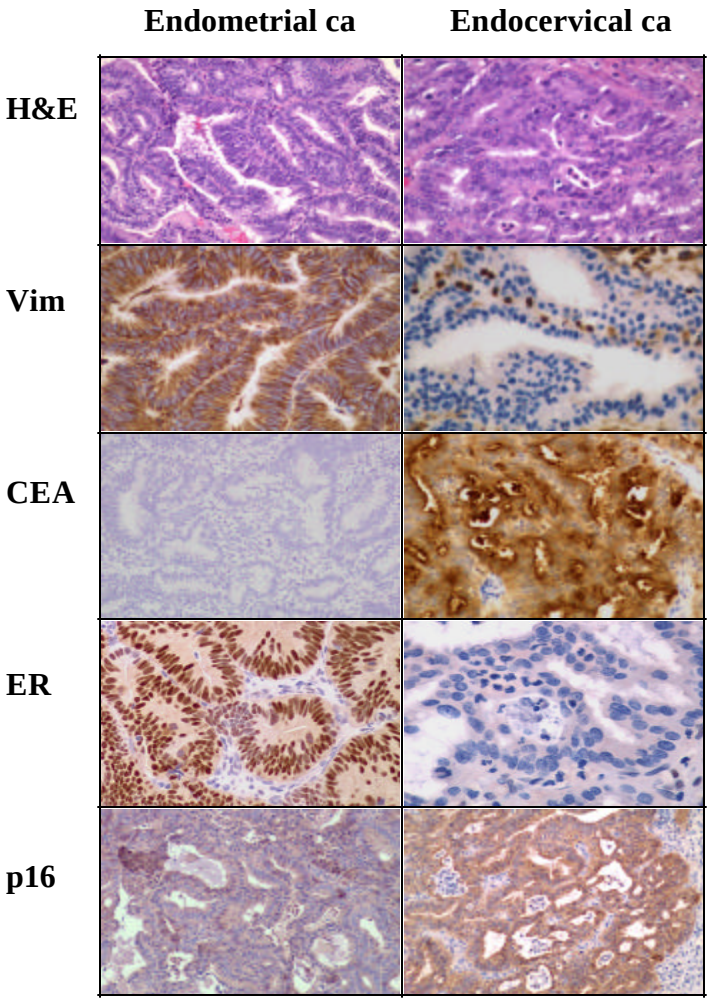
Update on Useful Immunohistochemical Markers

April 2003

by Rodney T. Miller, M.D., Director of Immunohistochemistry

This month we revisit the problem of distinguishing endocervical from endometrial adenocarcinomas, a topic that was previously addressed in the January 2002 issue of "Focus on Immunohistochemistry". Most surgical pathologists know very well that there is substantial morphologic overlap between these entities, but differences in therapeutic approaches necessitate attempts to distinguish these 2 tumors.

In the January 2002 issue of the International Journal of Gynecological Pathology, two papers addressed this problem. Castrillon et al (1) studied 30 endometrial adenocarcinomas and 29 endocervical adenocarcinomas, and included tumors with overlapping morphologic features. CEA was more common in endocervical adenocarcinomas (62%), than in endometrial adenocarcinomas (27%). The authors also noted that CEA appeared to be particularly useful for tumors that had endometrioid morphology, since only 14% of the endometrial endometrioid adenocarcinomas were CEA positive, in contrast to 67% of the endocervical adenocarcinomas with endometrioid morphology. 97% of the endometrial adenocarcinomas were vimentin positive, in contrast to only 7% of the endocervical adenocarcinomas. McCluggage et al (2) evaluated 30 endometrial adenocarcinomas and 26 endocervical adenocarcinomas. In their study, 93% of endometrial adenocarcinomas were strongly estrogen receptor (ER) positive, whereas focal weak ER positivity was noted in 38% of endocervical adenocarcinomas. Vimentin was diffusely positive in 97% of the endometrial adenocarcinomas, but in only 8% of the endocervical adenocarcinomas. Prior studies have reported ER in 70% of endometrial adenocarcinomas, in contrast to 10-20% of endocervical adenocarcinomas, vimentin reactivity in 50-81% of endometrial adenocarcinomas vs. <13% of endocervical adenocarcinomas, and CEA in 65-95% of endocervical adenocarcinomas. Staebler et al (4) studied 24 endometrial and 24 endocervical carcinomas, and found that only 1 of 24 (4.2%) endocervical carcinomas expressed both ER and PR. In contrast, 18 of 24 (75%) of endometrial carcinomas expressed ER, and 23 of 24 (95.8%) expressed PR. HPV in situ hybridization on formalin-fixed paraffin-embedded sections was also performed, which found HPV DNA in 16 of the 24 (66.7%) endocervical carcinomas, but in none of the 24 endometrial carcinomas. In light of the association of immunostaining of $p16^{(INK4a)}$ with high-risk HPV infection, one might surmise that immunostains for $p16^{(INK4a)}$ might also be of use in the differential diagnosis of endometrial adenocarcinoma vs. endocervical adenocarcinoma. Although immunohistochemical expression of $p16^{(INK4a)}$ has been described in both of these tumors, in a study of 24 unequivocal endometrial adenocarcinomas and 18 unequivocal endocervical adenocarcinomas, Ansari-Lari et al (6) reported at the recent 2003 USCAP meeting that the pattern of $p16^{(INK4a)}$ expression allowed distinction of the two tumors. All endocervical adenocarcinomas showed strong and diffuse $p16^{(INK4a)}$ immunostaining, with a mean of 94% of tumor cells reacting (range 90-100%). In contrast, the endometrial adenocarcinomas showed weaker staining with a patchy distribution, with a mean of 35% of tumor cells reactive (range 5-70%). In light of these results, a relatively small panel of immunostains including **vimentin, ER, PR, monoclonal CEA, $p16^{(INK4a)}$, and in situ hybridization for HPV** is



H&E and immunostains on cases of morphologically similar endometrial carcinoma (left column) and endocervical carcinoma (right column).

reasonable to address the problem of distinguishing endometrial from endocervical adenocarcinoma. Expected immunoreactivity in endometrial and endocervical adenocarcinoma is summarized in the Table.

In summary, the "classic" endometrial adenocarcinoma will be positive for vimentin, ER, PR, and show weak or patchy p16(INK4a), but negative for CEA and HPV. In contrast, the "classic" endocervical adenocarcinoma will be CEA positive, strongly and diffusely positive for p16(INK4a), and HPV positive but negative for vimentin, ER, and PR.

Antibody	Endocervical ca	Endometrial ca
Vimentin	- (7-8%+)	+ (>70-93%+)
CEA	65-95%+	usually -
ER	- (4-20%+, 38% weak)	strong+ in 67-90%
PR	- (4%+)	+ (96%)
p16	strong & diffuse mean 94%+ cells (90-100)	patchy mean 35%+ cells, (5-70)
HPV	67%+	-

References

1. Castrillon DH, Lee KR, Nucci MR: Distinction between Endometrial and Endocervical Adenocarcinoma: An Immunohistochemical Study. Int J Gyn Pathol 21 (1): 4-10, 2002.
2. McCluggage WG, Sumanthi VP, McBride HA et al: A Panel of Immunohistochemical Stains, Including Carcinoembryonic Antigen, Vimentin, and Estrogen Receptor, Aids the Distinction between Primary Endometrial and Endocervical Adenocarcinomas. Int J Gyn Pathol 21 (1): 11-15, 2002.
3. Zaino RJ: The Fruits of Our Labors: Distinguishing Endometrial from Endocervical Adenocarcinoma (Editorial). Int J Gyn Patho 21 (1): 1-3, 2002.
4. Staebler A, Sherman ME, Zaino RJ et al: Hormone Receptor Immunoreactivity and Human Papillomavirus In Situ Hybridization Are Useful for Distinguishing Endocervical and Endometrial Adenocarcinomas. Am J Surg Pathol 26 (8): 998-1006, 2002.
5. Kamoi S, AlJuboury MI, Akin M-R et al: Immunohistochemical Staining In the Distinction between Primary Endometrial and Endocervical Adenocarcinomas: Another Viewpoint. Int J Gyn Pathol 21: 217-223, 2002.
6. Ansari-Lari MA, Staebler, Ronnett BM: Distinction of Endocervical and Endometrial Adenocarcinomas: p16 Expression Correlated with Human Papilloma Virus (HPV) DNA Detection by In Situ Hybridization (ISH) Mod Pathol 16 (1): 180A (abstract #821), 2003.
7. Zhang X, Lin Z, Kim I: Immunohistochemical Profiles of Endometrial and Endocervical Adenocarcinomas. Mod Pathol 16(1): 217A (abstract #989), 2003.

Rodney T. Miller, M.D.
Director of Immunohistochemistry
214-237-1631 • Fax 214-237-1770
rmiller@propathlab.com

Prior Editions are available for download on our website.

PROPATH
8267 Elmbrook Drive, Suite 100 • Dallas, Texas 75247-4009
214-638-2000 • Toll Free: 800-258-1253 • Fax: 214-905-3457
www.propathlab.com