Anatomic pathology selected abstracts

Editors: Rouzan Karabakhtsian, MD, PhD, professor of pathology and director of the Women's Health Pathology Fellowship, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY; Shaomin Hu, MD, PhD, staff pathologist, Cleveland Clinic; S. Emily Bachert, MD, breast pathology fellow, Brigham and Women's Hospital, Boston; and Amarpreet Bhalla, MD, assistant professor of pathology, Albert Einstein College of Medicine, Montefiore Medical Center.

AMACR: a useful IHC marker of breast carcinoma with apocrine differentiation

May 2022—Carcinoma with apocrine differentiation is an androgen receptor-positive subset of triple-negative breast carcinoma. In addition to carcinoma with apocrine differentiation, other androgen receptor-positive triple-negative breast carcinomas occur, albeit less frequently. The authors found that α-methylacyl-CoA racemase (AMACR), also known as P504S, is overexpressed in carcinoma with apocrine differentiation and non-neoplastic apocrine metaplasia. They evaluated AMACR as a possible marker of carcinoma with apocrine differentiation. The authors used IHC to examine the expression of AMACR in carcinoma with apocrine differentiation and nonapocrine carcinomas and compared the findings to those generated for gross cystic disease fluid protein-15 (GCDFP-15). They evaluated 212 breast carcinomas: 39 carcinomas with apocrine differentiation, 28 ductal carcinomas in situ with apocrine morphology (ADCIS), and 145 nonapocrine breast carcinomas. AMACR was expressed in 38 of 39 (97.4 percent) carcinomas with apocrine differentiation and 27 of 28 (96.4 percent) ADCIS, consistent with the expression of GCDFP-15. However, in nonapocrine carcinomas, AMACR expression was observed in 32 of 145 (22 percent) lesions, whereas GCDFP-15 expression was observed in 91 of 145 (62.7 percent) lesions. For carcinoma with apocrine differentiation, AMACR was as sensitive as GCDFP-15 (both 97.1 percent) but more specific (77.9 percent versus 37.2 percent). In select cases, *AMACR* messenger RNA (mRNA) levels were determined quantitatively relative to that of TATA-binding protein mRNA. The relative mean levels of *AMACR* mRNA were 5.23, 1.33, and 0.60 in carcinomas with apocrine differentiation, nonapocrine carcinomas, and normal breast tissue, respectively. The authors concluded that their findings suggest that AMACR expression may be used to differentiate carcinoma with apocrine differentiation from nonapocrine carcinomas and that AMACR is a more sensitive marker of carcinoma with apocrine differentiation than GCDFP-15.

Nakamura H, Kukita Y, Kunimasa K, et al. α-methylacyl-CoA racemase: a useful immunohistochemical marker of breast carcinoma with apocrine differentiation. *Hum Pathol*. 2021;116:39–48.

Correspondence: Dr. Harumi Nakamura at nakamura-ha@mc.pref.osaka.jp

Value of p16 expression in the diagnosis of HPV-associated AIN

P16 is the most useful diagnostic marker for human papillomavirus-associated anogenital lesions. The pattern of p16 immunoreactivity in the cervix generally correlates with lesion severity. P16 expression in anal intraepithelial neoplasia (AIN) has been studied to a far lesser degree, so it has yet to be determined whether such a correlation holds true for AIN. The authors conducted a study in which they correlated the degree and pattern of p16 IHC results with the morphologic diagnoses of 1,000 anal squamous and transitional zone biopsy specimens. P16 IHC results were classified as block staining, partial staining, or negative using Lower Anogenital Squamous Terminology (LAST) criteria. Among 150 samples without morphologic evidence of AIN, p16 was negative in 85 percent and exhibited partial staining in 15 percent. AIN 1 lesions (n=400) revealed diverse p16 expression patterns: 28 percent negative, 35 percent partial staining, and 37 percent block staining. With AIN 2 (n=298), 89 percent were block staining, nine percent partial staining, and two percent negative. AIN 3 (n=152) revealed block staining (95 percent) and partial staining (five percent). For detecting AIN 2/3, p16 block staining yielded 91 percent sensitivity, 73 percent specificity, 80 percent positive predictive value, 91 percent negative predictive value, and a Youden index of 0.64. Combining block staining and partial staining slightly increased sensitivity (99 percent) and negative predictive value (98 percent) but significantly decreased specificity (43 percent), positive

predictive value (59 percent), and Youden index (0.42; $P<0.001$). The authors found that p16 immunoreactivity correlates with morphologic diagnosis of AIN. Block staining offers optimal diagnostic value for AIN 2/3. Caution is required since AIN 1 frequently exhibits block staining. The authors concluded that the prognostic value of p16 warrants further investigation.

Liu Y, McCluggage WG, Darragh TM, et al. p16 immunoreactivity correlates with morphologic diagnosis of HPV-associated anal intraepithelial neoplasia: a study of 1000 biopsies. *Am J Surg Pathol*. 2021;45:1573–1578.

Correspondence: Dr. Yuxin Liu at yuxin.liu@mountsinai.org

Cytoplasmic pattern p53 immunoexpression in pelvic and endometrial carcinomas with TP53 mutation

A cytoplasmic pattern of p53 IHC expression has been reported in a rare subset of pelvic and endometrial cancers that have a TP53 mutation involving domains affecting nuclear localization. The authors conducted a study in which they reported the clinicopathologic features of 31 cases of a TP53 mutation involving nuclear localization. The large study emphasizes practical strategies for recognizing this uncommon variant and distinguishing it from the p53 wild-type pattern. It also assesses the prognostic significance of TP53 mutation involving nuclear localization in the ovarian high-grade serous carcinoma (HGSC) cohort of The Cancer Genome Atlas database. Most of the 31 tumors in the study were advanced-stage pelvic or endometrial HGSC. All TP53 mutations were predicted to result in loss of function. The p53 overexpression pattern was present in six tumors, the p53 null pattern in three, and the p53 cytoplasmic pattern in 22. The pattern predominantly consisted of weak to moderate cytoplasmic staining in more than 95 percent of tumor cells and variable intensity nuclear staining involving a range of just a few tumor cells to just under 80 percent of cells. The p53 cytoplasmic pattern was observed in all tumors with TP53 mutation in the nuclear localization domain and 33 percent to 44 percent of tumors with a mutation in the adjacent tetramerization domain or nuclear exclusion sequence ($P<0.01$). P16 immunoexpression was present in 74 percent of tumors. In The Cancer Genome Atlas ovarian HGSC cohort, 41 (nine percent) of 471 nonredundant TP53-mutant cases had a nuclear localization domain, tetramerization domain, or nuclear exclusion sequence mutation, but there was no significant difference in survival when compared with the cases that had TP53 mutation outside those domains ($P>0.05$). P53 cytoplasmic staining merits classification as an aberrant result despite coexisting nuclear staining that in some cases may resemble the p53 wild-type pattern. While positive p16 immunostaining may be of value in confirming diagnostically challenging cases of p53 cytoplasmic staining, a negative result is uninformative. Molecular testing for TP53 mutation should be considered.

Rabban JT, Garg K, Ladwig NR, et al. Cytoplasmic pattern p53 immunoexpression in pelvic and endometrial carcinomas with TP53 mutation involving nuclear localization domains: an uncommon but potential diagnostic pitfall with clinical implications. *Am J Surg Pathol*. 2021;45(11):1441–1451.

Correspondence: Dr. J. Rabban at joseph.rabban@ucsf.edu