Anatomic Pathology Selected Abstracts, 2/15

Editors: Michael Cibull, MD, professor emeritus, University of Kentucky College of Medicine, Lexington; Rouzan Karabakhtsian, MD, attending pathologist, Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; Thomas Cibull, MD, dermatopathologist, Evanston Hospital, NorthShore University HealthSystem, Evanston, Ill.; and Rachel Stewart, DO, resident physician, Department of Pathology and Laboratory Medicine, University of Kentucky.

Alteration of ARID1A gene, PI3K-Akt pathway, and ZNF217 gene in ovarian clear cell carcinoma

AT-rich interactive domain 1A (ARID1A) is a subunit of switch/sucrose nonfermentable (SWI/SNF) complex. Recently, alterations of the ARID1A gene, phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) pathway, and *zinc-finger protein* 217 (ZNF217) gene have been identified as frequent molecular genetic changes in ovarian clear cell carcinoma. The relationships between these events have not been studied and integrated in the same cohort. The authors conducted a study to determine the correlation between these events and other clinicopathological factors, including the prognostic impact of these factors. They collected 68 ovarian clear cell carcinoma cases and subjected them to immunohistochemistry testing for ARID1A, SMARCA2, SMARCA4, SMARCB1 and phosphatase and tensin homolog (PTEN), mutation analysis for the *phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha* (PIK3CA) gene, and fluorescence in situ hybridization for ZNF217 amplification. They then analyzed the correlations between ARID1A expression, P13K-Akt pathway, ZNF217 amplification, and other clinicopathological factors. Loss of ARID1A expression was present in 35 (52 percent) cases, and loss of SMARCA2 expression occurred in one case. SMARCA4 and SMARCB1 expression were preserved in all cases. PIK3CA mutations were present in 23 (34 percent) cases, and loss of PTEN expression occurred in eight (12 percent) cases. Alterations in the PI3K-Akt pathway (PIK3CA mutations or loss of PTEN expression) were found in 42 (62 percent) cases. ZNF217 amplification was detected in 21 (31 percent) cases. Loss of ARID1A expression was significantly related to younger patient age (P=0.048), PI3K-Akt pathway activation (P=0.046), and ZNF217 amplification (P=0.028). All of the clinicopathological factors were not prognostic factors for ovarian clear cell carcinoma after multivariate analysis, except International Federation of Gynecology and Obstetrics staging (P=0.001). The results of the study showed that loss of ARID1A expression usually coexists with PI3K-Akt pathway activation or ZNF217 amplification, or both. Synergic effects of loss of ARID1A and PI3K-Akt pathway activation, as well as ZNF217 amplification, may be related to the development of ovarian clear cell carcinoma.

Huang HN, Lin MC, Huang WC, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations and ZNF217 amplification in ovarian clear cell carcinoma. *Mod Pathol.* 2014;27:983–990.

Correspondence: Dr. K. T. Kuo at pathologykimo@gmail.com

MED12 and HMGA2 mutations: independent genetic events in uterine leiomyoma and leiomyosarcoma

Recent identification of somatic MED12 mutations in most uterine leiomyomas brings a new perspective to the study of the tumorigenesis of leiomyomas. The authors were particularly interested in the correlation of MED12 and HMGA2 gene products in leiomyomas and leiomyosarcomas with and without MED12 mutations. To address these issues, they examined MED12 mutations in a large cohort of usual type leiomyomas (178 cases) and uterine leiomyosarcomas (32 cases). They found that 74.7 percent (133 of 178) of leiomyomas had MED12 mutations, which was consistent with several independent studies. In contrast, only 9.7 percent (three of 32) of leiomyosarcomas harbored MED12 mutations. Expression analysis by Western blot and immunohistochemistry revealed that those leiomyomas with complex MED12 mutations had significantly lower protein products than the matched myometrium. Interestingly, most leiomyosarcomas without MED12 mutations also had very low levels of

MED12 expression in comparison to the matched myometrium. These findings suggest a potential functional role for MED12 in benign and malignant uterine smooth muscle tumors. When the authors further examined the HMGA2 expression in all leiomyomas and leiomyosarcomas, they found that HMGA2 overexpression was present exclusively in those leiomyomas with no MED12 mutation, accounting for 10.1 percent (18 of 178) of total leiomyomas and 40 percent (18 of 45) of non-MED12 mutant leiomyomas. Twenty-five percent (eight of 32) of leiomyosarcomas had HMGA2 overexpression, and no MED12 mutations were found in HMGA2-positive leiomyosarcomas. These findings strongly suggest that MED12 mutations and HMGA2 overexpression are independent genetic events that occur in leiomyomas, and they may act differently in the tumorigenesis of uterine leiomyomas.

Bertsch E, Qiang W, Zhang Q, et al. MED12 and HMGA2 mutations: two independent genetic events in uterine leiomyoma and leiomyosarcoma. *Mod Pathol.* 2014;27(8):1144–1153.

Correspondence: Dr. T. Kurita at t-kurita@northwestern.edu or Dr. J. J. Wei at jianjun-wei@northwestern.edu

Human papillomavirus genotyping and p16 expression as prognostic factors in carcinoma of the anal canal

Carcinomas of the anal canal are strongly associated with human papillomavirus. Expression of p16 is used as a surrogate marker of such infection. The authors conducted a retrospective study in which they evaluated human papillomavirus (HPV) genotyping and p16 expression as prognostic markers of overall survival and disease-specific survival in patients diagnosed with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. HPV genotyping polymerase chain reaction (high-risk subtypes 16, 18, 31, 33, 45, 52, and 58) and immunohistochemical expression of p16 were analyzed using paraffin-embedded tumor biopsies from 143 anal carcinomas. The patients were treated with combined chemoradiotherapy or radiotherapy alone. HPV16 was detected in 81 percent of the tumors, followed by HPV33 (5.1 percent), HPV18 (2.2 percent), and HPV58 (0.7 percent). P16 positivity was found in 92.9 percent of the tumors. In univariable survival analysis, HPV positivity was significantly correlated with improved overall survival (74 percent versus 52 percent; P=0.036) and disease-specific survival (84 percent versus 52 percent; P=0.002), and p16 positivity was significantly correlated with improved overall survival (76 percent versus 30 percent; P=0.001) and disease-specific survival (85 percent versus 30 percent; P<0.001). In multivariable Cox analysis that included HPV status, p16 status, gender, T stage, N stage, and treatment, p16 positivity remained an independent prognostic factor for overall survival (hazard ratio [HR], 0.07; 95 percent confidence interval [CI], 0.01–0.61; P=0.016) and disease-specific survival (HR, 0.07; 95 percent CI, 0.01–0.53; P=0.011). The authors concluded that p16 positivity is an independent prognostic factor for overall and disease-specific survival in patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal.

Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, et al. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. *J Clin Oncol.* 2014;32:1812–1817.

Correspondence: Dr. Eva Serup-Hansen at eva.serup-hansen@regionh.dk