Anatomic Pathology Selected Abstracts, 12/14

Anatomic pathology abstracts editors: Michael Cibull, MD, professor of pathology, University of Kentucky, 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.

Value of autopsies in the era of high-tech medicine

Although the autopsy is still the gold standard for quality assessment of clinical diagnoses, autopsy rates have declined to less than 10 percent. The authors conducted a study to investigate the value of autopsies in the era of high-tech medicine by determining the frequency of discrepancies between clinical and autopsy diagnoses. The authors classified all adult autopsy cases (n=460) performed at the Symbiant Pathology Expert Centre in Holland, in 2007 and from 2012 to 2013, as having major or minor discrepancy or total concordance. They analyzed the roles of possible contributory factors and assessed the role of microscopic examination in identifying cause of death. Major and minor discrepancies were found in 23.5 percent and 32.6 percent of the classifiable autopsies, respectively. The most commonly observed major discrepancies were myocardial infarction, pulmonary embolism, and pneumonia. Improper imaging and discontinuation of active treatment were significantly associated with a higher and lower frequency of major discrepancies, respectively. Comparing 2007 and 2012 to 2013, the frequency of minor discrepancies significantly increased from 26.8 percent to 39.3 percent. Final admission length of more than two days was significantly associated with a lower frequency of class III minor discrepancies. Microscopic examination contributed to establishing cause of death in 19.6 percent of the cases. The authors concluded that discrepant findings persist at autopsy, even in the era of high-tech medicine. Therefore, autopsies should still serve as an important part of quality control in clinical diagnosis and treatment. Learning from individual and system-related diagnostic errors can help improve patient safety.

Kuijpers CC, Fronczek J, van de Goot FR, et al. The value of autopsies in the era of high-tech medicine: discrepant findings persist. *J Clin Pathol.* 2014;67:512–519.

Correspondence: Dr. Mehdi Jiwa at m.jiwa@symbiant.nl

Keratin 17 in premalignant and malignant squamous lesions of the cervix safety.

Most previously described immunohistochemical markers of cervical high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma may help improve diagnostic accuracy but have minimal prognostic value. The authors conducted a study to identify and validate novel candidate biomarkers that could potentially improve diagnostic and prognostic accuracy for cervical HSIL and squamous cell carcinoma. Microdissected tissue sections from formalin-fixed, paraffin-embedded normal ectocervical squamous mucosa, low-grade squamous intraepithelial lesion (LSIL), HSIL, and squamous cell carcinoma sections were analyzed by mass spectrometry-based shotgun proteomics for biomarker discovery. The diagnostic specificity of candidate biomarkers was subsequently evaluated by immunohistochemical analysis of tissue microarrays. Among 1,750 proteins identified by proteomic analyses, keratin 4 and keratin 17 showed reciprocal patterns of expression in the spectrum of cases ranging from normal ectocervical squamous mucosa to squamous cell carcinoma. Immunohistochemical studies confirmed that keratin 4 expression was significantly decreased in squamous cell carcinoma compared with the other diagnostic categories. By contrast, keratin 17 expression was significantly increased in HSIL and squamous cell carcinoma compared with normal ectocervical squamous mucosa and LSIL. Keratin 17 was also highly expressed in immature squamous metaplasia and endocervical reserve cells but was generally not detected in mature squamous metaplasia. Furthermore, high levels of keratin 17 expression were significantly associated with poor survival of squamous cell carcinoma patients (hazard ratio, 14.76; P=0.01). The authors concluded that the level of keratin 17 in squamous cell carcinoma may help identify patients who are at greatest risk for cervical cancer mortality.

safety.

Escobar-Hoyos LF, Yang J, Zhu J, et al. Keratin 17 in premalignant and malignant squamous lesions of the cervix: proteomic discovery and immunohistochemical validation as a diagnostic and prognostic biomarker. *Mod Pathol.* 2014;27(4):621–630.
safety.

Correspondence: K. R. Shroyer at kenneth.shroyer@stonybrook medicine.edu

Hormone receptor-positive and hormone receptor-negative tumors in HER2-positive breast cancer

The clinical behavior of human epidermal growth factor receptor 2-positive breast cancer, including pathologic complete response rate and pattern of relapse and metastasis, differs substantially according to hormone receptor (HR) status. The authors investigated various histopathologic features of human epidermal growth factor receptor 2 (HER2)-positive breast cancer and their correlation with HR status. They retrospectively analyzed tumors from 450 HER2-positive breast cancer patients treated with chemotherapy and one year of trastuzumab. HR-negative/HER2-positive tumors showed higher nuclear grade, less tubule formation, higher histologic grade, frequent apocrine features, diffuse and abundant lymphocytic infiltration, strong HER2 immunohistochemical staining (3+), higher average HER2 copy number and HER2/CEP17 ratio, absence of HER2 genetic heterogeneity, and greater p53 expression than HR-positive/HER2-positive tumors. An inverse correlation was observed between estrogen receptor or progesterone receptor Allred score and average HER2 copy number or HER2/CEP17 ratio. The percentage of ductal carcinoma in situ (DCIS) within the tumor was negatively correlated with estrogen receptor Allred score but positively correlated with average HER2 copy number and HER2/CEP17 ratio. Pathologic tumor size and DCIS percentage also showed a significant inverse correlation. Ratio of metastatic to total examined lymph node number was significantly correlated with average HER2 copy number and HER2/CEP17 ratio. High pT stage (hazard ratio, 2.370; P=0.027), presence of lymphovascular invasion (hazard ratio, 2.806; P=0.005), and HR negativity (hazard ratio, 2.202; 1.074–4.513; P=0.031) were independent prognostic indicators of poor disease-free survival. The authors concluded that HR-positive/HER2-positive and HR-negative/HER2-positive breast cancer showed distinct histopathologic features that may be relevant to their clinical behavior.

Lee HJ, Park IA, Park SY, et al. Two histopathologically different diseases: hormone receptor-positive and hormone receptor-negative tumors in HER2-positive breast cancer. *Breast Cancer Res Treat.* 2014;145(3):615–623.

Correspondence: G. Gong at gygong@amc.seoul.kr

Lung cancer histologic and immunohistochemical heterogeneity in the era of molecular therapies

On the basis of seminal studies in the 1980s, appreciable histologic heterogeneity, ranging from 45 percent to 70 percent of cases, may be encountered in lung cancer. However, the epidemiologic and histologic landscape of lung cancer in the last three decades has radically changed. The authors conducted a study in which 172 consecutive surgically resected primary lung carcinomas evaluated from 2010 to 2012 were sampled and examined according to current histologic classifications. A positive preoperative biopsy was also available in 129 cases. Major histologic heterogeneity (a single tumor showing at least two histologic types) and minor histologic heterogeneity (a single tumor showing one histologic type but at least two different growth patterns) were evaluated in all cases. Immunohistochemical heterogeneity—that is, aberrant staining—was also assessed on positive biopsies and surgical specimens using a panel of markers of adenocarcinoma (TTF-1, napsin, and CK7), squamous cell carcinoma (p63 and CK5/6), and neuroendocrine differentiation (chromogranin and synaptophysin). Overall, major and minor histologic heterogeneity on resections were disclosed in four percent (seven cases) and 50.6 percent (87 cases), respectively, whereas just one case of minor heterogeneity (pleomorphic carcinoma) was observed on biopsies. Minor heterogeneity was limited to adenocarcinomas (82.6 percent; 81 of 98 cases) and sarcomatoid

carcinomas (six pleomorphic types among eight sarcomatoid carcinomas). Immunohistochemical heterogeneity was recorded in 22.6 percent of the cases, with expression of p63 and CK5/6 in a subset of adenocarcinomas (25 cases; 25.5 percent), CK7 in 17.4 percent of squamous cell carcinomas, and synaptophysin in six cases of non-neuroendocrine tumors (four percent; six of 155 cases). The high rate of adenocarcinomas, accounting for 57 percent of the 172 consecutively resected lung cancers (98 cases), reflects the new scenario of thoracic oncology and may explain the significant lower rate of major histologic heterogeneity (four percent) and higher frequency of different architectural patterns (minor heterogeneity) that the authors found in lung cancer when compared with previous studies.

Cadioli A, Rossi G, Costantini M, et al. Lung cancer histologic and immunohistochemical heterogeneity in the era of molecular therapies: analysis of 172 consecutive surgically resected, entirely sampled pulmonary carcinomas. *Am J Surg Pathol.* 2014;38(4):502–509.

Correspondence email not provided.

Complete androgen insensitivity syndrome: factors influencing gonadal histology

Patients with complete androgen insensitivity syndrome are at increased risk for developing gonadal germ cell cancer. Residual androgen receptor activity and abnormal gonadal location may influence the survival of atypical germ cells and the development of other histopathological features. To assess this, the authors evaluated 37 gonads from 19 patients ranging in age from three months to 18 years who had complete androgen insensitivity. Histological abnormalities were examined using hematoxylin-and-eosin–stained sections and sections stained for POU5F1 and KITLG, markers of early changes in germ cells at risk for malignant transformation. Hamartomatous nodules, Leydig cell hyperplasia, decreased germ cells, tubular atrophy, and stromal fibrosis were more pronounced as age increased ($P<0.001$). Expected residual androgen receptor activity acted as a positive predictor only for nonmalignant germ cell survival in postpubertal patients ($P<0.05$). Immunohistochemical studies indicated that delayed maturation of germ cells was present in three patients, whereas intermediate changes that occurred between delayed maturation and intratubular germ cell neoplasia, designated pre-intratubular germ cell neoplasia, were identified in four cases. Intratubular germ cell neoplasia was observed in one patient. Neither POU5F1 nor KITLG expression was dependent on expected residual androgen receptor activity. An independent effect of inguinal versus abdominal position of the gonads was difficult to assess because inguinal gonads were present primarily in the youngest individuals. The authors concluded that many histological changes occur increasingly with age. Expected residual androgen receptor activity contributes to better survival of the general germ cell population in postpubertal age; however, it did not seem to play an important role in survival of the germ cells at risk for malignant transformation (defined by POU5F1 positivity and KITLG overexpression) in complete androgen insensitivity. Comparison of the high percentage of patients in this study who were carrying germ cells with delayed maturation or pre-intratubular germ cell neoplasia with previously reported cumulative risk of tumor development in adult patients indicates that not all such precursor lesions in complete androgen insensitivity will progress to invasive germ cell cancer.

Kaprova-Pleskacova J, Stoop H, Brüggenwirth H, et al. Complete androgen insensitivity syndrome: factors influencing gonadal histology including germ cell pathology. *Mod Pathol.* 2014;27:721–730.

Correspondence: Dr. J. Kaprova-Pleskacova at kapr.jana@seznam.cz

Predictive value of IASLC/ATS/ERS classification of lung adenocarcinoma in tumor recurrence and patient survival

The authors investigated the pattern of recurrence of lung adenocarcinoma and the predictive value of histologic classification in resected lung adenocarcinoma using the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification system. The

histologic classification of 573 patients undergoing resection for lung adenocarcinoma was determined according to the IASLC/ATS/ERS system. The percentage of each histologic component—lepidic, acinar, papillary, micropapillary, and solid—was recorded. The pattern of recurrence of those components and their predictive value were investigated. The predominant histologic pattern was significantly associated with gender ($P<0.01$), invasive tumor size ($P<0.01$), T status ($P<0.01$), N status ($P<0.01$), tumor-node-metastasis stage ($P<0.01$), and visceral pleural invasion ($P<0.01$). Micropapillary- and solid-predominant adenocarcinomas had a significantly higher probability of developing initial extrathoracic-only recurrence than did other types ($P<0.01$). The predominant pattern group—micropapillary or solid versus lepidic, acinar, or papillary—was a significant prognostic factor in overall survival (OS, $P<0.01$), probability of freedom from recurrence ($P<0.01$), and disease-specific survival ($P<0.01$) in multivariable analysis. For patients receiving adjuvant chemotherapy, solid-predominant adenocarcinoma was a significant predictor for poor overall survival ($P=0.04$). The authors concluded that in lung adenocarcinoma, the IASLC/ATS/ERS classification system has significant prognostic and predictive value with respect to death and recurrence. Solid-predominant adenocarcinoma was also a significant predictor in patients undergoing adjuvant chemotherapy. Prognostic and predictive information is important for stratifying patients for aggressive adjuvant chemoradiotherapy.

Hung JJ, Yeh YC, Jeng WJ, et al. Predictive value of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in tumor recurrence and patient survival. *J Clin Oncol.* 2014;32(22):2357–2364.

Correspondence: Dr. Wen-Hu Hsu at whhsu@vghtpe.gov.tw