Department of Pathology

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General Summary

The objective of our research in the Department of Pathology is to morphologically investigate the causes of disease and to evaluate morphological changes. We used human tissue samples resected at autopsy and surgery or obtained at biopsy. These samples were examined with light microscopy, electron microscopy, morphological measurement, immunohistochemical staining, and molecular pathological techniques.

Research Activities

Research on the gastrointestinal tract

1. Budding, lymphatic invasion, and venous invasion are known risk factors for lymph-node metastasis in cases of colorectal cancer with submucosal invasion. We studied the relations between combinations of budding, lymphatic invasion, and venous invasion and the presence or absence of lymph-node metastasis in 22 endoscopically resected submucosal cancers for which the presence or absence of lymph-node metastasis was determined (Katsushika Medical Center, from January 2012 through October 2015). Lymph-node metastasis was present in 2 of the 22 lesions. The lymph-node metastasis was associated with the combinations of budding + lymphatic invasion and of budding + lymphatic invasion + venous invasion.

2. To evaluate the histopathological characteristics of villous adenomas, 74 lesions with villous component in part of the adenoma were identified by reviewing colorectal epithelial tumors that were stored at Katsushika Medical Center (2009-2016). Regions of tubular component were found in all of these lesions. Regions of villous component, tubular component, and normal glands were manually resected from 1 lesion with villous capillaries, and the presence or absence of mutations of the Guanin nucleotide binding protein, alpha stimulating gene (GNAS) complex locus gene was compared. The results showed that *GNAS* mutations can be found in regions of villous component, whereas no mutations were found in regions of tubular component.

Research on female genital organs

1. In patients with ovarian clear-cell carcinoma associated with underlying endometriosis, AT-rich interactive domain 1A gene (ARID1) abnormality might be related to both carcinogenesis and tumor progression. Interleukin 6 provides control signals for *ARID-1*, but

no correlation was found between *ARID-1* abnormalities and interleukin 6 expression in ovarian clear-cell carcinoma.
2. Recent studies have shown that high-grade serous carcinoma (HGSC), usually considered a primary tumor arising in the ovaries or peritoneum, can be due to the metastasis of fallopian tube cancer to the ovary or peritoneum and that the organ with the largest mass is not necessarily the site of the primary tumor. In patients with a clinical diagnosis of bilateral ovarian cancer, detailed examination of surgical specimens of the fimbriae of the fallopian tube showed HGSC and contiguous intraepithelial serous adenocarcinoma in the fimbriae of the fallopian tube. Primary cancer of the fimbriae of the fallopian tube was diagnosed. In cases of HGSC, the primary lesion can be identified with detailed observation and examination of the fimbriae of the fallopian tube.

Research on urogenital organs
1. Primary lesions and metastatic lesions of urothelial cancer were immunostained (human epidermal growth factor receptor [HER2], p53, and Ki-67), and HER2 was evaluated with the use of immunohistochemical staining according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists. In patients with 2+ immunohistochemical staining, fluorescence in-situ hybridization was performed to assess gene amplification. The results showed that 3+ staining was present in 17% of cases. Gene amplification was found with fluorescence in-situ hybridization in 6 cases with 2+ staining. The rate of positivity for HER2 did not differ significantly between patients with metastasis and those without metastasis.
2. Continuing from the previous year, we studied the clinical histopathological characteristics of prostate cancers of the anterior and transition zone and those of the posterior and marginal zone. Immunostaining for phosphatase and tensin homologue (PTEN) and serine peptidase inhibitor, Kazal type 1 (SPINK1) was performed to compare expression levels in each zone. In addition, *SPINK1* expression was compared between cancers that were positive or negative for erythroblast transformalion specific related gene (ERG). In prostate cancers of the anterior and transition zone, the incidence of *PTEN* loss was significantly lower than that in prostate cancers of the posterior and marginal zone. The expression of *SPINK1* did not differ significantly. The expression of *ERG* and that of *SPINK1* were mutually exclusive.

Research on the liver
1. In patients with primary biliary cirrhosis who underwent several biopsies, histological changes were assessed according to Nakanuma's classification to investigate whether such changes correlate with changes in biochemical data. A correlation between clinical findings (changes in biochemical data) and pathological findings was often seen in patients in whom changes in pathological findings were inconsistent with clinical data. Histological evidence of inflammation and chronic nonsuppurative destructive cholangitis were seen in some patients despite improvements in such variables as alkaline phosphatase and γ-glutamyl transpeptidase. During the follow-up of patients with primary biliary cirrhosis both blood chemical testing and liver biopsy should be performed if possible.

Research on the mammary gland

1. Data on approximately 300 cases of benign and borderline lesions were collected and computerized. The pathological diagnosis of some intraductal lesions varied from benign (hyperplasia) to malignant (noninvasive ductal carcinoma), depending on the pathologist. On immunostaining for actin, p63, and CD10, positive staining at intratubular sites of hyperplasia (distinctly biphasic) was associated with benign papilloma. However, positive staining only around the ducts (myoepithelium present) was associated with great variation in the lesion being diagnosed as benign or malignant.

Molecular pathological research

1. We investigated new responsible genes related to the development and progression of primary lung cancer. To discover the locations of these genes, microsatellite instability (MSI) analysis was performed with the polymerase chain reaction and 19 DNA markers at chromosome 8p to evaluate a total of 306 cases of lung adenocarcinoma, squamous-cell carcinoma, or neuroendocrine tumor. The incidence of MSI was found to be 20% at 8p23.2, 51% at 8p23.1, 24% at 8p22, and 15% at 8p21. The incidence of MSI was significantly higher at 8p23.1 than at other regions. In particular, the incidence of MSI at DNA marker *D8S1819* was high in each histologic type of lung cancer, suggesting that a responsible gene related to the development of lung cancer is present at 8p23.1.

Publications

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