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 by means such as light microscopy, electron microscopy, morphological measurement, immunohistochemical staining, and molecular pathological techniques.

Research Activities

Research on the Digestive Tract

1. Surgical specimens of small bowel Crohn's disease were split to map the locations of epithelioid granulomas and ulcers and to determine the distribution of granulomas in the wall and the positional relations between granulomas and ulcers. Among a total of 385 granulomas, 1.3% were located in the mucosa, and 19.8% were located in the submucosa. Overall, 97.1% of the granulomas were located within 10 mm from ulcers in a horizontal direction. To accurately diagnose Crohn's disease, biopsy specimens including the submucosa should be taken from regions within 10 mm from ulcers.
2. Since 2016, we have compared endoscopic findings with histological findings of ulcerative colitis. We have obtained 537 biopsy specimens from 191 patients. The degree of inflammation tended to correlate with endoscopic findings and histologic findings and more strongly correlated with histologic findings. In severely inflamed mucosa associated with endoscopic evidence of erosions and ulcers, basal plasmacytosis was histologically found in 58.5% of cases. Basal plasmacytosis was considered an important finding suggesting the presence of active inflammation.
3. We studied the histologic characteristics of colorectal neuroendocrine tumors. In particular, we examined the relations of tumor grade based on the 2010 World Health Organization (WHO) Classification of Gastrointestinal Tumors to vascular invasion and outcomes. Surgically and endoscopically resected colorectal carcinoid tumors were stained with elastica–van Gieson (EVG) stain and immunostain (CD31, D2–40, and MIB–1 antibodies) in addition to hematoxylin and eosin stain. Each lesion was classified according to tumor grade, and the tumor diameter, invasion depth, submucosal invasion distance, number of nuclear division cycles, Ki67 index, and lymphovascular invasion were assessed. The relations of lymphovascular invasion and other risk factors to outcomes were then studied. In our hospital, we are currently analyzing data on 160 cases consist-

ing of 139 endoscopically resected cases and 21 surgically resected cases.
4. To investigate predictors of lymph-node metastasis in patients with colorectal submucosal cancer, we studied specimens stained with hematoxylin and eosin obtained from 124 patients with colorectal submucosal cancer from 2009 through 2015. After excluding patients with double cancer invading the submucosa or deeper regions, 102 patients were extracted. Representative sections underwent special staining and immunohistochemical staining. Data on the following variables were extracted: the presence or absence of depressions, intramucosal growth patterns (non-polypoid growth, polypoid growth), the measured depth of invasion (less than 1,000 μm, 1,000 μm or greater), histologic type of the invasion site, the presence or absence of tumor budding (+/−), lymphovascular invasion: lymphatic invasion and venous invasion (+/−), the locations and numbers of lymphovascular invasion sites in the primary lesion, the presence or absence of a mixture of poorly differentiated adenocarcinoma and mucinous carcinoma, tumor budding, and types of intravascular carcinomas (sporadic tumors, nested tumors). We are planning to perform multivariate analysis in the future.

Research on the kidney
1. A prospective, multicenter, collaborative study organized by the Ministry of Health, Labour and Welfare Immunoglobulin A (IgA) Nephropathy Subcommittee
A total of 847 cases of IgA nephropathy were classified into active and chronic types according to the histologic severity classification. The histologic subclassification of IgA nephropathy was found to be useful for selecting patients eligible for tonsillectomy steroid treatment.
2. Three-dimensional structure of glomerulonephritis assessed using a scanning electron microscope
Serial block-face scanning electron microscopy (SBF-SEM), which was introduced at the National Institute for Physiological Science, was used to analyze cases of IgA nephropathy. IgA nephropathy was broadly classified into 2 types according to the destructive patterns of the glomerular basement membrane: a type with mesangial cells invading the glomerular epithelium and a type with epithelial cells invading the glomerular endothelium. As a result, the interactions between podocytes and mesangial cells were found to be caused by direct contact between cells and not by paracrine factors.

Research on the urogenital system
1. In patients who had prostate cancer with a Gleason score of 3+4=7, we examined whether the proportion of Gleason pattern 4 in biopsy specimens and other biopsy parameters are useful for predicting outcomes after total prostatectomy. Patients in whom the proportion of Gleason pattern 4 was 5% or higher in biopsy specimens had higher risks of malignancy and biochemical recurrence than did patients with a Gleason score of 3+3=6.
2. In 148 patients with urothelial cancer, we examined the relations of the presence or absence of human epidermal growth factor receptor-2 (HER2) overexpression and the immunohistochemical subtype to clinicopathological factors. HER2 protein overexpression or gene amplification was found in 14% of patients. All patients were immunohistochemically classified into 2 subtypes: basal subtype and luminal subtype of urothelial

cancer. HER2 protein overexpression or gene amplification was found in 4% of basal subtype and in 22% of luminal subtype.

Research on the female genital system

1. Continuing from last year, we participated in an international joint symposium that was held to clarify the validity and problems of the WHO Histologic Classification of Cervical Carcinoma, which was revised in 2014. On the basis of a review of the histologic images and the results of immunohistochemical staining and outcome surveys, we developed an algorithm to identify problems related to the histologic classification and immunohistochemistry at the time of diagnosis.
2. To assess the diagnostic accuracy and outcomes of endometrial sarcoma in our hospital, we performed joint research with the Department of Obstetrics and Gynecology and found that endometrial sarcoma can occur in young females. Histopathologically, such cases are being shown to be characterized by the presence of a mixture of well-differentiated components and poorly differentiated components.
3. We studied malignant tumors developing in patients with ovarian seromucinous borderline tumors (SMBT). In 16 cases of tumors associated with SMBT among patients in whom ovarian cancer was diagnosed in our hospital, we pathologically examined factors such as the histologic type of malignant tumors, invasive pattern, tumor stage, and the presence or absence of concurrent lesions. Most malignant tumors associated with SMBT were found to be endometrioid. Seromucinous carcinoma was rare. The rate of infiltrative-type invasion was higher than that in previous studies. The pathological diagnosis of the majority of lesions was stage I disease according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

Research on molecular pathology

1. Analysis of chromosomal instability related to the development and progression of lung cancer

Microsatellite makers were used in several candidate chromosomal regions of primary lung cancers to comprehensively perform chromosomal instability analysis, focusing on the chromosome 3p allele. Based on the results, we confirmed chromosomal regions that were most strongly associated with the development and progression of each histologic type of lung cancer, with the final goal of identifying new responsible genes existing in candidate chromosomal regions. To select heterozygous DNA polymorphic markers for microsatellite analysis in Japanese patients with lung cancer, we analyzed normal lung tissue in 16 Japanese patients with lung cancer. Polymerase-chain-reaction and loss-of-heterozygosity (PCR-LOH) analysis was comprehensively performed, using microsatellite markers related to 321 known genes existing in all regions of the short arm of chromosome 3 (3p12-26.3). Among 321 DNA polymorphic markers, 312 markers (97%) could be detected as PCR products. Among 312 DNA polymorphic markers, only 47 markers (15%) were heterozygous. Japanese have fewer informative microsatellite markers than Westerners. This phenomenon is similarly observed in other chromosomal regions, such as 4p, 6q, 8p, 9q, 10q, and 13q. This is considered a genomic characteristic of Japanese or Asians. By analyzing cancer tissue in patients with lung cancer, the local-

ization of responsible genes in candidate chromosomal regions might be able to be more efficiently clarified.

Others

1. To determine age-related changes in the radius of the hepatic lobules, histometric analysis of liver tissue was performed in patients who underwent autopsy. The radius (y) of the hepatic lobule increased with age (x). In patients 40 years or older, R2 calculated by the formula, y=0.0032 x+0.3167, was about 0.65, indicating a relatively strong correlation.
2. We have encountered autopsy cases of fulminant group A streptococcal infection of the right lower limb. Many bacteria were present in the infected site, but there was nearly no inflammation. Previous studies demonstrated that fulminant group A streptococcal infection is associated with no local inflammatory response or only a very weak inflammatory response. In the present study, we did not investigate M proteins. However, previous studies reported that the inflammatory response is inhibited by factors such as the presence of hyaluronic acid capsules, M proteins, C5a peptidase, and nuclease.

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