Department of Pathology

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General summary

The research projects of our department focus on the pathogenesis, histogenesis, morphogenesis, and clinical pathology of nonneoplastic and neoplastic human disease by means of light and electron microscopy, morphometry, immunohistochemistry, and gene analysis.

Research Activities

Pathology of the liver

The proliferating bile ductules of the liver in obstructive jaundice were examined with immunohistochemistry for CK7, CK19, and a human hepatocyte marker (Hepatocyte) to elucidate the origin of the ductules. Immunohistochemical double-staining for CK7 and Hepatocyte was also performed. Most liver cells were positive for Hepatocyte but not for CK7, whereas the epithelial cells of bile ducts and ductules were positive for CK7 but not for Hepatocyte. In cases of prolonged jaundice, many liver cells expressed both CK7 and Hepatocyte. These findings indicate that a part of liver cells showing such coexpression could change directly into epithelial cells of the proliferating bile ductules. We concluded that the proliferating bile ductules might derive from hepatocytes by direct transdifferntiation, not by indirect transdifferentiation matapasia.

The lymphatic channels of portal areas in the normal liver were examined by histologic reconstruction using serial sections and immunohistochemical studies for a lymph-vessel marker (D2-40). The lymphatic channels were divided into 2 systems on the basis of function. One is a system of lymphatic channels that run along arteries. Its role is to collect surplus interstitial fluid that leaks through the arterial wall to decrease arterial pressure. The role of the other system is to collect various substances produced in the portal areas and transport them to lymph nodes.

We continued to study the role of oxidative stress in the pathogenesis and evolution of nonalcoholic fatty liver disease. The distribution and intensity of oxidative stress markers were immunohistochemically examined with sections cut from paraffin blocks without degreasing. The results showed that both the nuclei and cytoplasm of liver cells were extensively positive for DNA oxidative stress markers (8-hydroxydeoxyguanosine and thymidineglycol). On the other hand, liver cells were negative for a fat oxidative stress marker (hexanoyl-lysine).

The cross-sectional area of the parenchyma, portal tracts, portal veins, arteries, and bile

ducts and the cross-sectional area of parenchyma per portal area in normal liver were determined with morphometry. The area ratio of the parenchymal portion was 93.5%. The mean sectional area of the parenchymal area per portal tract was 0.10 cm^2. The figure was constant regardless of age.
Nonalcoholic steatohepatitis associated with hepatocellular carcinoma was studied.

Renal pathology
Mitochondrial nephropathy with genetically proven mitochondrial disease was examined with light and electron microscopy. Granular swollen epithelial cells (GSECs) were found among the distal and collecting tubules. Ultrastructural analysis showed accumulation of abnormally shaped mitochondria in GSECs. Genetic analysis of GSECs revealed that their mutant load was significantly greater than that of normal-appearing epithelial cells within the same sample.
Histopathological variables listed in the Oxford international classification and the Japanese classification of IgA nephropathy were further investigated to improve interobserver reproducibility. On the basis of the results, the histological classification was revised.
Histologic reevaluation of specimens of 1,545 renal cell carcinomas collected in the department was continued with revised general rules for clinical and pathological studies of renal cell carcinoma. The file contains 5 cases associated with polycystic kidney, 4 cases with bronchial metastasis, and 13 cases of bilateral renal cell carcinoma.
The relationship between renal function and pathologic findings of renal biopsy specimens was examined in various renal diseases and transplanted kidneys.

Gastrointestinal pathology
Risk factors for metastasis of submucosal invasive colon cancers to lymph nodes were investigated using 203 surgically resected submucosal invasive colon cancers. In particular, vessel permeation and budding of cancer cells as risk factors were analyzed in this study. Special stains such as CD31, CD34, and D2–40 immunostains and elastica van Gieson stain were used to evaluate blood and lymphatic vessel permeation. Multivariate analysis showed that lymphatic permeation and venous permeation were significant risk factors (odds ratios of 3.6 and 7.5, respectively). Univariate logistic analysis revealed that budding was related to lymph node metastasis, lymphatic permeation, and venous permeation (odds ratios of 3.4, 3.9 and 2.6, respectively). These results suggest that budding is deeply involved in lymphatic and venous permeation. In addition, a likelihood-ratio test showed no significant differences between a model that included budding and a model that excluded budding. These results further suggest that vessel permeation is the best risk factor for predicting lymph node metastasis.

Urogenital pathology
We continued a pathologic study of prostatic cancer. Akt is a major protein of the intracytoplasmic signaling system. Expression of Akt and phosphorylated Akt was examined immunohistochemically in cells of precancerous tissue of the prostate, microscopic prostate cancer, and clinical prostate cancer. The results suggest that the

expression of phosphorylated Akt is related to clinical stage, cancer invasion of the seminal vesicle, and a high level of prostate-specific antigen.
A total of 716 testicular tumors collected in the department were studied clinicopathologically and immunohistochemically. There were 5 cases of spermatocytic seminoma, 67 cases of tumors greater than 100 mm in diameter, 11 cases of bilateral tumors, and 13 cases of adenomatoid tumors.

Gynecological pathology

Early hydatidiform moles with a gestational age of less than 12 weeks were examined to establish histologic criteria.

Breast pathology

Breast tumors on the borderline between benignancy and malignancy were collected and analyzed clinicopathologically. The results showed that neuroendocrine ductal carcinoma in situ is difficult to diagnose.
Overexpression of human epidermal growth factor receptor (HER2) was evaluated immunohistochemically (Hercep test), and HER2 gene amplification was simultaneously determined with fluorescence in situ hybridization (FISH) in breast cancer. Three of 39 cases showed a discrepancy between overexpression on immunohistochemical studies and gene amplification by means of FISH.

Oncology

Genetic analysis of lung and liver cancers was continued to identify candidate susceptibility inhibitor genes that play an important role in carcinogenesis and progression.

Publications

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