

## Department of Pathology

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### General Summary

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

### Research Activities

#### *Pathology of the liver*

Oxidative stress in alcoholic fatty liver, nonalcoholic fatty liver, and nonalcoholic steatohepatitis in the early and late stages was investigated immunohistochemically. 8-Hydroxydeoxyguanosine was used as a marker of oxidative stress. This stress marker was expressed in fine granular fashion, especially around fat droplets in the cytoplasm, by hepatocytes in the early stage and was expressed in fine to rough granular fashion in the cytoplasm of macrophages in the late stage. This finding indicates that oxidative stress in the late stage is involved in the transition from fatty liver to steatohepatitis.

We continued an immunohistochemical study of the origin of proliferative ductules in cholestatic liver damage caused by obstructive jaundice. On the basis of the results of immunohistochemical studies with cytokeratin (CK) 7, CK19, and hepatocyte antigen, we have concluded that proliferating ductules originate from hepatocytes by direct transdifferentiation. In the present study coexpression of CK7 and hepatocyte antigen was confirmed by immunofluorescence. In the cases of successful biliary drainage we found marked decreases in the numbers of hepatocytes coexpressing CK7 and hepatocyte antigen, cessation of ductular proliferation, disappearance of proliferating ductules, and remaining proliferating ductules strikingly similar to preexisting ductules. Such histologic changes indicate restructuring of the biliary drainage system, that is, the process of self-assembly of histologic structures in a thermodynamic nonequilibrium system.

We continued a study with a histologic reconstruction method of the process of fibrosis in nonalcoholic steatohepatitis. As the extent of fibrosis progressed, especially in the middle stage of fibrosis, it became more and more evident that bandlike fibrous connections between central vein areas in adjacent lobules surrounded the portal tracts. In contrast to the change in centrilobular areas, the portal area showed a tendency to be preserved until this stage. It is also noteworthy that arteries developed strikingly in fibrotic areas around the veins in the middle stage.

### *Renal pathology*

Additional research focusing on pathologic variables was performed to compare the Oxford classification of immunoglobulin (Ig) A nephropathy with the Japanese classification. In this study a Japanese cohort was investigated retrospectively using the Oxford research method. We found that the Oxford classification of IgA nephropathy was not applicable to a Japanese cohort because of the differences in some variables of both classifications. A new international classification is expected to be applicable to a Japanese cohort.

Interobserver reproducibility between 4 Japanese pathologists was assessed by means of intraclass correlation coefficients with reference to the Oxford and the Japanese classifications of IgA nephropathy. Specimens used were from 90 cases with IgA nephropathy from 15 institutions. Good reproducibility was obtained for the histologic severity of the Japanese classification and the Oxford classification.

Cystic renal cell carcinoma was investigated. Lesions with cystic changes occupied the renal cell carcinoma in various proportions up to 100%. Cases in which more than 50% of cystic renal cell carcinoma was occupied by cystic lesions showed no metastasis and a good prognosis.

Age-associated renal histologic changes were investigated. Forty-five kidneys obtained at autopsy were used for morphometric analyses. Results were as follows. The mean density of glomeruli (per  $\text{cm}^2$ ) was more than 4,000 in fetuses but then gradually decreased to 10 to 20 in adults in their 20s. The mean diameter of glomeruli was 60  $\mu\text{m}$  in newborns, 100  $\mu\text{m}$  in infants, 130  $\mu\text{m}$  in persons in their 20s, and 160  $\mu\text{m}$  in persons in their 60s and 70s. The mean ratio of the glomeruli to the cortical area was 0.6% in infants and 0.2% to 0.3% in teenagers and older groups. The average number of tubules was 2,000 per  $\text{mm}^2$  in newborns and 1,000 per  $\text{mm}^2$  in teenagers and older age groups.

### *Gastrointestinal pathology*

Risk factors for the metastasis of esophageal superficial carcinoma to lymph nodes were investigated using 203 surgically resected tumors. Our aim was to expand the application of endoscopic mucosal resection and to avoid subsequent redundant surgical resection. Lymphatic channels were immunohistochemically stained with D2-40, and blood vessels were stained with Elastica-van Gieson stain and immunohistochemical stains for CD31 and CD34. Multivariate statistical analysis showed that both blood vessel invasion and lymphatic invasion, which were diagnosed immunohistochemically, were most strongly correlated with lymph node metastasis. The negative predictive value was 94.6%.

### *Lung pathology*

Central emphysema was investigated with thick histologic sections (50, 70, 100, and 150  $\mu\text{m}$ ) stained with Masson's Trichrome and Elastica-van Gieson to clarify the morphogenesis. Microscopic examination showed the stepwise histologic features of alveolar destruction. In the early stage we recognized solitary fenestrae of various size in an alveolar wall in the center of the acinus. They fused to form larger fenestrae that occupied the whole area of alveolar walls. As the alveolar change progressed, only the

strands containing thick elastic fibers were left in the alveolar area. On the other hand, the same change took place in the alveolar wall attached to the bronchovascular bundles. As a result, the bronchioles came to lose the support of alveolar walls. The lung structure is normally supported by the tension of the elastic and collagen fiber continuum (the fiber system). It is conceivable that the diseased alveolar area gradually changed to cysts owing to both the destruction of the fiber system and the effect of pressure generated by air flow.

#### *Urogenital pathology*

Pathologic stage pT1 urinary bladder cancer showed a wide range of histologic features, from microinvasion to widespread submucosal invasion. Cases of pT1 urinary bladder cancer were classified into 3 groups, that is, pT1a, pT1b, and pT1c, according to the depth of invasion. We analyzed the differences among the 3 groups concerning the period of no symptoms, the period of no deterioration, and the survival time. The period of no deterioration was significantly shorter in the pTc group than in the pTa group. We conclude that the subclassification is useful for prognostic evaluation of patients.

#### *Breast pathology*

A total of 191 cases of borderline malignancy of breast cancer were investigated with immunohistochemical studies for actin, p63, and CD10. If cells positive for these markers were distributed throughout the entire intraductal proliferative lesion, papilloma was diagnosed. However, if positive cells were localized along the margin of the intraductal proliferative lesion, determining whether the lesion was benign or not was difficult. Further investigation is needed to solve this problem.

#### *Oncology*

We have previously clarified that 8q22-23.2 is a candidate chromosomal region involved in the development and metastasis of hepatocellular carcinoma. This time we tried to identify candidate genes within that region of the chromosome. Gene analysis, however, identified no significant mutation in more than 10 candidate genes, including DLC1 and MTUS1. Possible future subjects of investigation to solve the problem are messenger RNA and protein expression involved in gene function.

#### *Other topics*

We reported an autopsy case of Fabry disease. Deposition sites of glycolipids were identified with immunohistochemical staining for Gb3. These sites included cardiac muscles and epithelial cells of the renal glomerulus and tubules and endocrine organs, such as the pituitary gland, adrenal gland, and pancreas. The latter had not yet previously been identified as deposition sites. Therefore, further investigation is needed to confirm deposition in the latter sites.

We reported a case of pulmonary meningioma that appeared after an intracranial meningioma had been resected. Both meningiomas were benign (grade 1). We compared our case to similar cases previously reported. On the basis of the clinical course and the morphology of tumors, we concluded that the pulmonary meningioma was not a primary

tumor but rather was a metastasis from the intracranial meningioma.

## Publications

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for a phase III, multicenter, randomized, controlled trial. *BMC Cancer* 2010; **10**: 572.

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**Kamoi S<sup>1</sup>, Ohaki Y<sup>1</sup>, Mori O<sup>1</sup>, Fukunaga M, Takeshita T<sup>1</sup> (Nippon Med Sch).** Determining best potential predictor during high-dose progestin therapy for early staged and well-differentiated endometrial adenocarcinoma using semiquantitative analysis based on image processing and immunohistochemistry. *J Nihon Med Sch* 2011; **78**: 84-95.

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## Reviews and Books

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