

Department of Pathology

Hiroshi Hano, *Professor*
Akihiko Sakata, *Professor*
Masahiro Ikegami, *Associate Professor*
Hiroyuki Takahashi, *Associate Professor*
Yukiko Kanetsuna, *Assistant Professor*
Tomoe Lu, *Assistant Professor*

Masaharu Fukunaga, *Professor*
Masafumi Suzuki, *Associate Professor*
Satoru Chiba, *Associate Professor*
Koichi Nomura, *Associate Professor*
Tohru Harada, *Assistant Professor*
Masakazu Komine, *Assistant Professor*

General Summary

The aim of our research in the Department of Pathology is to elucidate, on the basis of morphology, pathogenesis and morphological changes. The materials used are human specimens from autopsies, surgical resections, and biopsies. These materials are examined with light microscopy, electron microscopy, morphometry, immunohistochemistry and molecular pathology.

Research Activities

Pathology of liver

1. Pathology of nonalcoholic steatohepatitis

We performed studies until the last fiscal year on how tissue injury in the precirrhotic stage of nonalcoholic steatohepatitis (NASH) changes over time. This research involved 3-dimensional histological reconstruction of the liver using serial sections and focused on 3-dimensional changes in liver fibrosis and the course of blood vessels. We found progression of fibrosis around the central veins, with connections to fibrosis around adjacent central veins, thus leading to fibrous bridging. Extension of these changes throughout the liver resulted in the formation of fibrosis surrounding the portal tracts. However, even at this stage, the fibrous bridging between the central veins and portal tracts was limited to a few sites. The reason fibrous bridging was limited was that the portal vascular structure was preserved, with little injury involving the portal tracts or parenchyma. Over time, arteries developed in fibrotic areas around the central vein, but these arteries clearly arose from arteries in the portal tracts.

The incidence of ballooning degeneration of hepatocytes in NASH varied among individual cases. Ballooning degeneration was prominent in central areas in the hepatic lobule and parenchymal margins surrounding fibrotic lesions and in areas of fibrous bridging between the central areas in the hepatic lobules and portal tracts. These findings suggest that progression of fibrosis in NASH is associated with ballooning degeneration as well as with inflammation. Considering that inflammatory changes are relatively mild and sporadic in NASH, we speculate that the ballooning degeneration that occurs before fibrosis is important in the mechanism of fibrosis.

2. Findings in the background liver in non-B, non-C hepatocellular carcinoma

This study focused on past medical history and the histopathological changes of the liver in areas other than hepatocellular carcinoma (HCC) in 36 patients with non-B, non-C

HCC. Excessive alcohol use, NASH, and lifestyle-related diseases, such as obesity and diabetes, were thought to be involved. However, histopathological examination found that some livers had extensive remodeling, as seen in hepatic fibrosis and cirrhosis; some livers had mild, nonspecific damage; and other livers had an almost normal appearance. In other words, the background liver lesions varied considerably.

3. Expression of prominin 1 (CD133) protein in HCC genesis and metastasis

The protein prominin 1 is constitutively expressed in normal, nonneoplastic hepatocytes in human fetuses and adults. The expression of prominin 1 protein in the normal liver is attenuated or lost during the malignant transformation of hepatocytes. Loss of the intrinsic physiological function of prominin 1 is thought to be associated with a high likelihood of HCC. However, in the process of HCC metastasis, no substantial changes in prominin 1 expression were observed. Therefore, there is probably no direct causal association between prominin 1 and cancer metastasis.

4. The origin of proliferative ductules in obstructive jaundice

In early obstructive jaundice (up to 14 days after onset), bile ductules appear near the portal tracts and are intermingled with hepatic cords. In some cases, these bile ductules are also intermingled with preexisting interlobular bile ducts. In late obstructive jaundice (more than 14 days after onset), these bile ductules continue to proliferate, fibrosis occurs, the older bile ductules are surrounded by fibrosis, and there is a morphologically similar appearance to preexisting interlobular bile ducts.

On the basis of these morphological findings, we performed immunostaining for bile ductule CK7 and a hepatocyte marker. The bile ductules were positive for CK7, and the hepatocytes were positive for the hepatocyte marker. In obstructive jaundice, hepatocytes with coexpression of CK7 and the hepatocyte marker increased over time. Later, hepatic cords that also contained stem cells expressing only the hepatocyte marker were prominent, and in some areas, there was contiguity between the hepatic cords and proliferative ductules. This finding suggests a close association among these 3 structures. We conclude that bile ductules are formed from hepatocytes via hepatocytes that coexpress both CK7 and hepatocyte markers.

Gastrointestinal pathology

1. Risk factors for metastasis from small cancers of the colon to lymph nodes were examined in 203 submucosal invasive carcinomas and 62 advanced carcinomas 20 mm or less in diameter. For submucosal invasive carcinoma, 6 risk factors (macroscopic depression, intramucosal growth, submucosal invasiveness, invasive histologic type, budding, and vessel invasion) were established, and multivariate analysis was performed. In particular, vessel invasion was accurately evaluated with immunostaining for D2-40 and CD31 and Elastica van Gieson staining. The most important risk factor for metastasis in submucosal invasive carcinoma was vessel invasion, as evaluated with D2-40, CD31 and Elastica van Gieson staining.

Urological pathology

1. Renal pathology

We analyzed the morphology of renal tissue. Postmortem tissue specimens were

examined from the kidneys of 43 patients without known lesions. Renal growth and changes with aging were evaluated on the basis of arterial size, arterial wall thickness, and morphological changes in the glomeruli. We found that inner and outer diameters of arteries increased with age and that the glomerular capillaries and mesangial cells increased with age after the age of 10 years. We also found that in patients with high kidney weight, the numbers of morphologically preserved glomeruli and renal tubules per unit area were smaller.

2. Renal cell carcinoma

We evaluated cases of cystic renal cell carcinoma (RCC). There was a morphological spectrum ranging from tumors being entirely cystic to being partially cystic. In particular, when the cystic area was 50% or more, there were no metastases, and the prognosis was good. Among 25 patients with bilateral RCC, 7 patients had metastases from the contralateral kidney, and 8 patients had lesions that had clearly developed separately.

3. Prostate cancer

The relationship between pAKT and ETS-related gene (ERG) expression in clinical carcinoma was evaluated. pAKT was expressed in about half of Japanese men with prostate cancer, and ERG was expressed in about 25%. There was a negative correlation between the expression frequency of pAKT and that of ERG. This finding suggests that these 2 pathways of malignant transformation are independent. In addition, the frequency of ERG expression in Japanese men was only about half that in Western men and suggests ethnic differences in the malignant transformation pathway. In a study of latent prostate carcinoma, such data as the incidence of latent carcinoma, cancer volume, and age in recent autopsy cases were compared with previously accumulated latent carcinoma data (from the 1980s). This comparison showed a doubling in the incidence of cancer and a particular increase in larger tumors.

Gynecological pathology

1. We examined the histopathology of endometrioid adenocarcinoma treated with hormone therapy (medroxyprogesterone acetate) to preserve fertility (maintain the ability to become pregnant). We found decreased cellular atypia, signs of glandular secretion, and decidual tissues in the stroma. However, the basic pattern of glandular proliferation showed few changes. Live births were achieved in a small number of cases. However, no histological diagnostic criteria for cancer after hormone therapy or guidelines concerning when to discontinue treatment have been established. These are issues for further investigation.

2. Diagnostic significance and histogenic significance of TSSC3 and p57 staining in trophoblastic disease.

Breast pathology

1. We reviewed 191 breast lesions that were on the borderline between benignancy and malignancy. There was intraobserver disagreement about the diagnosis in some patients and a discrepancy in diagnosis ranging from benign (hyperplasia) to malignant (ductal carcinoma in situ). In particular, there were strong tendencies for discrepancies in

diagnosis among cases in which myoepithelium was present only in the lumen borders of intraductal lesions.

2. Comparison between immunostaining results and fluorescence in-situ hybridization analysis for human epidermal growth factor receptor 2 testing in breast cancer.

Other pathology

1. We evaluated dermokine expression in tumor lesions derived from oral stratified squamous epithelium. We found that dermokine expression differed between normal oral mucosa and the skin and that expression in tumor lesions was closely related to tumor differentiation.

2. We reported pathological findings in an autopsy case of Chagas disease.

3. We examined systemic changes due to graft-versus-host disease after bone marrow transplantation.

Publications

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