

Department of Pathology

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General Summary

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

Research Activities

Hepatology

We studied pathological changes of blood vessels in chronic viral hepatitis. To elucidate the pathogenesis of changes to the portal vein, such as stenosis and disappearance, we examined the immunohistochemical expression of E-selectin, intercellular adhesion molecule (ICAM), and endothelial nitric oxide synthase (eNOS) of endothelial cells of the portal veins in biopsy specimens of the liver in cases of chronic viral hepatitis. E-selectin and ICAM are adhesion molecules that are involved in leucocyte recruitment and inflammation. eNOS is involved in vasorelaxation, platelet aggregation, and cardiovascular homeostasis. Whereas ICAM was positive in few cases, E-selectin was expressed by endothelial tissue in all cases. eNOS expression was observed in the endothelial cells of the portal and central veins. Expression of E-selectin and ICAM and the level of activity of eNOS are considered to be involved in the development of portal vein damage.

We studied ductular reactions and progenitor cells of the liver in cases of obstructive jaundice by means of histologic reconstruction and immunohistochemistry. Histologic reconstruction focusing on ductular reactions showed bile ductular proliferation with a conspicuous complicated appearance, mainly located around the original portal tract. Biliary-type cells, hepatocytes, cytokeratin-7-positive hepatocytes, and intermediate cells were identified immunohistochemically. The results are being analyzed.

Damage and repair of the DNA of hepatocytes caused by oxidative stress in regenerative nodules of liver cirrhosis were investigated immunohistochemically. The results of immunohistochemical studies showed that 8-hydroxydeoxyguanosine as a marker of oxidative stress was expressed frequently and extensively and that proliferating cell nuclear antigen was also expressed frequently. Hepatocytes positive for proliferating cell nuclear antigen were inferred to be under repair.

Renal pathology

Nephritis related to myeloperoxidase antineutrophil cytoplasmic autoantibodies (MPO-ANCA) was analyzed clinicopathologically. Angitis tended to develop in elderly patients and was related to the serum value of C-reactive protein. Histologic examination revealed numerous hemosiderin deposits in the tubules and interstitial tissue. Hemosiderosis was correlated with active glomerular and tubular lesions and the severity of hematuria.

Histologic examination in cases of chronic rejection of renal transplants revealed that endothelial cells of the glomerular tuft were replaced by cells with many caveolae, i.e., invaginations of the plasma membrane. This replacement was thought to cause proteinuria.

Specimens of kidneys with IgA nephropathy collected from universities and national hospitals were examined clinicopathologically to establish new criteria for the prognosis of IgA nephropathy. As a result of this examination, some points to be revised were discussed from the view point of the histopathology of IgA nephropathy.

We continued our histological re-evaluation of specimens of renal cell carcinoma in our department with revised general rules for clinical and pathological studies of renal cell carcinoma. Cases of renal cell carcinoma accompanied by various degrees of cystic lesions were studied clinicopathologically. We found that cases with cystic lesions occupying more than 50% of the whole kidney had no metastasis and a good prognosis.

Gastrointestinal pathology

The characteristics of mucin produced by cancer of the gastric cardia were examined. We found that differentiated adenocarcinoma that produces gastric-type mucus tended to invade and change to a poorly differentiated type. We are comparing these findings to those of gastric cancer developing in other regions.

The relation between the sprout-like growth pattern at the forward edge of cancer and lymphatic invasion was examined in colorectal cancer with submucosal invasion.

Gynecologic pathology

The reproducibility of the histologic diagnosis of endometrial carcinoma was examined. Histologic findings of endometrial carcinoma treated with hormone therapy were examined to establish criteria for the efficacy of medroxyprogesterone acetate treatment. Using a mouse model of antiphospholipid antibody syndrome, we examined morphological changes of the microcirculation of the placenta and kidney. Whereas no particular changes were found with light microscopy, electron microscopy disclosed the irregular arrangement of endothelial pores of the glomerular capillary and splitting of the basement membrane of blood vessels of the placenta. These findings strongly suggest the initial histologic changes of antiphospholipid antibody syndrome.

Urogenital pathology

Clinicopathological studies of prostatic carcinoma continued. Specimens of prostatic carcinoma in Japanese patients were evaluated with the revised Gleason grading system in 2005. The results suggest that separate scoring is clinicopathologically useful.

Lung pathology

The analysis of clinicopathologic data obtained from 787 autopsy cases of primary lung cancer was completed.

Oncology

Analysis of loss of heterozygosity in 33 surgically resected specimens of liver cell carcinoma was performed with microsatellite markers at chromosome 8. The results suggest that candidate susceptibility genes for liver cell carcinoma reside at 8p23-22.

The inhibitory effects of the histone deacetylase inhibitor trichostatin A on cell lines of renal cell carcinoma were examined. The results showed that trichostatin A has a strong inhibitory effect on the proliferation of cultured carcinoma cells. Candidate susceptibility genes for this effect were investigated with DNA chip analysis and other methods.

Other

Hemorrhagic cyst of the right atrium was studied clinicopathologically.

Histologic examination of spindle cell tumor of the soft tissue was performed to evaluate the grade of malignancy.

Publications

Fukunaga M. Atypical ovarian endometriosis. *Pathol Case Rev* 2006; **11**: 38-42.

Fukunaga M, Fujiwara Y¹, Naito Z¹ (¹Nippon Med Sch). Hepatoid carcinoma with serous component of the fallopian tube: a case report with immunohistochemical and ultrastructural studies. *Int J Gynecol Pathol* 2006; **25**: 233-8.

Goda K, Tajiri H, Ikegami M, Urashima M, Nakayoshi T, Kaise M. Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma. *Gastrointest Endosc* 2007; **65**: 36-46.

Harada T, Kawakami M, Hano H, Ujita M, Saito Y, Odaka M, Sato S, Akiba T. Analysis of lymph node metastasis in primary lung cancer (3rd report) (in Japanese). *Tokyo Jikeikai Ikadaigaku Zasshi (Tokyo Jikeikai Med J)* 2007; **122**: 1-10.

Hano H, Takagi I, Nagatsuma K, Lu T, Meng C, Chiba S. An autopsy case showing massive fibrinoid necrosis of the portal tracts of the liver with cholangiographic findings similar to those of primary sclerosing cholangitis. *World J Gastroenterol* 2007; **28**: 639-42.

Kanetsuna Y, Hirano K¹, Nagata M (Univ Tsukuba), Gannon AM¹, Takahashi K¹, Harris CR¹, Breyer DM¹, Takahashi T¹ (¹Vanderbilt Univ). Characterization of diabetic nephropathy in a transgenic model of hypoinsulinemic diabetes. *Am J Physiol Renal Physiol* 2006; **291**: F1315-

22.

Komine K, Kohno Y. Histopathological examination of thymic gland : with special reference to myasthenia gravis. (in Japanese) *Tokyo Jikeikai Ikadaigaku Zasshi (Tokyo Jikeikai Med J)* 2006; **121**: 177-8.

Lu W, Takahashi H, Furusato B (AFIP), Maekawa S (Ogawa Red Cross Hosp), Ikegami M, Sudo A, Egawa S, Hano H. Allelotyping analysis at chromosome arm 8p of high-grade prostatic intraepithelial neoplasia and incidental, latent, and clinical prostate cancers. *Genes Chromosomes Cancer* 2006; **45**: 509-15.

Lu T, Hano H, Meng C, Nagatsuma K, Chiba S, Ikegami M. Frequent loss of heterozygosity in two distinct regions, 8p23.1 and 8p22, in hepatocellular carcinoma. *World J Gastroenterol* 2007; **28**: 1090-7.

Matsushita K¹, Ochiai T¹, Shimada H¹, Kato S², Ohno T², Nikaïdo T, Yamada S², Okazumi S¹, Matsubara H¹, Takayama W¹, Ishikura H¹ (¹Chiba Univ), Tsuji H² (²Nat'l Inst Radiol Sci). The effects of carbon ion irradiation revealed by excised perforated intestines as a late morbidity for uterine cancer treatment. *Surg Today* 2006; **36**: 692-700.

Oikawa H¹, Oka K¹, Nagakura S¹, Fukunaga M, Sando N¹, Kashimura J¹ (¹Mito Saiseikai General Hosp), Hakozaiki H (Fukushima Rosai Hosp). Spindle and giant cell type undifferentiated carcinoma arising in the common bile duct: a case report. *Pathol Res Pract* 2007; **203**: 179-84.

Shida T¹, Furuya M¹, Nikaido T, Hasegawa M¹, Koda K¹, Oda K¹, Miyazaki M¹, Kishitani Y¹, Ishikura H¹ (¹Chiba Univ). Sonic hedgehog-Gli1 signaling pathway might become an effective therapeutic target in gastrointestinal neuroendocrine carcinomas. *Cancer Biol Ther* 2006; **5**: 153-8.

Tozaki M, Fukuda K, Suzuki M. Dynamic high-spatial-resolution MR imaging of invasive ductal carcinoma: influence of histological scirrhous component on MR descriptors. *Magn Reson Med Sci* 2006; **5**: 137-46.

Wakui S, Yokook, Takahashi H, Muto T, Suzuki Y, Kanai Y, Hano H, Furusato M, Endou H. Prenatal 3,3',4,4',5-pentachlorobiphenyl exposure modulates induction of rat hepatic CYP 1A1, 1B1, and AhR by 7,12-dimethylbenz[α]anthracene. *Toxicol Appl Pharmacol* 2006; **210**: 200-11.

Wakui S, Yokook, Muto T, Suzuki Y, Takahashi H, Furusato M, Hano H, Endou H, Kanai Y. Localization of Ang-1, -2, Tie-2, and VEGF expression at endothelial: pericyte interdigitation in rat angiogenesis. *Lab Invest* 2006; **86**: 1172-84.

Walker DP (Little Rock), Ferrario F (San Carlo Borromeo Hosp), Joh K, Bonsib MS (Indiana Univ Med Center). Dense deposit disease is not a membranoproliferative glomerulonephritis. *Mod Pathol* 2007; **20**: 605-16.

Yamamoto I, Yamaguchi Y, Yamamoto T, Hosoya T, Horita S¹, Tanabe K¹, Fuchinoue S¹, Teraoka S¹, Toma H¹ (¹Tokyo Women's Med Univ). A pathological analysis of lymphatic vessels in early renal allograft. *Transplant Proc* 2006; **38**: 3300-3.