

Department of Pathology

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General Summary

The research objectives in the Department of Pathology include the investigation of pathogenesis and morphological changes based on morphology. The materials used include human specimens from autopsies, surgical resections, and biopsies. These materials are examined with light microscopy, electron microscopy, morphometry, immunohistochemistry, and molecular pathology.

Research Activities

Research in liver disease

1. In the evaluation of primary biliary cirrhosis (PBC), Scheuer's classification and Ludwig's classification have traditionally been used, but Nakanuma's classification has now recently been proposed. An increase in serum anti-gp210 antibodies in patients with PBC is associated with more frequent progression to liver failure and lower survival rates. In the present research, we have evaluated PBC activity and staging using Nakanuma's classification and compared this with Scheuer's classification. We have also examined histological findings in high and low anti-gp210 antibody groups to investigate how anti-gp210 antibody levels are related to histological findings. In Nakanuma's classification, various histological findings in PBC are scored and totaled to comprehensively assess activity and staging. The problem with this classification is that it requires complex evaluation. In the high anti-gp210 antibody group, the rate of chronic nonsuppurative destructive cholangitis, the fibrosis score, and stage were all higher. This finding confirms a strong correlation between these antibodies and the progression to liver failure.
2. Serial sections were prepared from biopsy specimen blocks from patients with early chronic hepatitis. Through histologic reconstruction of these serial sections, we examined the type of injury that occurs in portal vein branches in chronic hepatitis. We found that in early chronic hepatitis, these portal vein branches are lost within areas of fibrosis.
3. Using image analysis, we measured arterial density, arterial wall thickness, and the inner/outer diameters of arterial lumens in normal livers to investigate their relationships with aging. However, we found no obvious association with age. We also examined the number of nuclei in hepatocytes in fixed areas of the hepatic parenchyma and found that hepatocyte size increased with aging.
4. With a focus on protein metabolism in nonalcoholic steatohepatitis, we examined

metabolic impairment in needle biopsy liver specimens from the perspective of oxidative stress and glycation stress. Dityrosine, a protein oxidation marker, was uniformly distributed as granules in hepatocytes. These granules were densely distributed around areas of fibrosis and in hepatocytes near the portal tract. Carboxymethyl lysine, a glycoxidation marker, showed a similar distribution and was even more densely distributed in phagocytic macrophages.

Research in kidney disease

1. The Oxford International Classification for immunoglobulin (Ig) A nephropathy differs from the histological severity classification in Japan (Japanese Classification). We performed a retrospective study of cases in Japan using the Oxford International Classification. This study included 233 adult patients with IgA nephropathy over a follow-up period of 127 months. With a 50% decline in renal function or progression to end-stage renal disease as an endpoint, Cox simple regression and multiple regression analyses were performed. We found that extracapillary lesions and the severity of interstitial fibrosis were independent indicators of renal prognosis. However, in the Oxford Classification, interstitial fibrosis, segmental sclerosis, mesangial hypercellularity, and endocapillary proliferation, rather than extracapillary lesions, were indicators of a poor prognosis. The difference between classifications is attributed to differences in follow-up period, patient age, initial estimated glomerular filtration rate, and restrictions in protein.

Research in gastrointestinal disease

1. For neuroendocrine neoplasms of the colon, the World Health Organization gastrointestinal tumor classification (2010) recommends diagnosis based on a combination of mitotic number and Ki-67 index of the lesions; these neoplasms are classified as neuroendocrine tumors grade 1 and grade 2 and neuroendocrine cancer. Therefore, we reviewed lesions at our hospital previously diagnosed as carcinoid tumors, applied the new diagnostic criteria, and examined the pathological features. The lesions included 98 colon carcinoid tumors that had been endoscopically resected. We found that higher-grade neuroendocrine tumors were larger and had higher rates of lymphatic and venous permeations.

2. We investigated risk factors for lymph node metastasis of small colon cancers in 203 patients with submucosal (SM) cancer and 62 patients with more advanced carcinoma measuring ≤ 20 mm. Six risk factors for lymph node metastasis in SM cancer were established: macroscopic depression, intramucosal growth (polypoid growth or nonpolypoid growth type), depth of SM invasion (SM1 or SM2/3), histological invasion type (well/moderate or poor), budding, and lymphatic and venous permeations assessed using immunostaining. These factors were subjected to multivariate analysis. The most important risk factor was lymphatic and venous permeations (odds ratio: 9.5). In almost all cases without lymphatic and venous permeations, lymph node metastasis was absent. The findings were similar for advanced carcinoma ≤ 20 mm. The results suggest that for lesions without lymphatic and venous permeations, the risk of lymph node metastasis is low.

Research in genitourinary disease

1. Immunohistologic studies were performed in 8 patients with inflammatory myofibroblastic tumors of the bladder. Immunostaining for anaplastic lymphoma kinase was positive in all patients, and in 1 of these patients, p53 was diffusively positive and mitoses were prominent. This patient had multiple recurrences during follow-up, and histopathologic examination showed changes with a high grade of atypia. Therefore, staining for p53 may be useful as a marker for malignancy in inflammatory myofibroblastic tumors.
2. In 201 Japanese men with prostate cancer, we examined clinicopathologic factors according to cancer location. Eighty-three patients had anterior cancer, 72 had posterior cancer, and 46 had other types of cancer. Compared with Western countries, Japan has a higher prevalence of anterior prostate cancer. The distribution of Gleason scores and pT stages differed significantly between anterior and posterior cancers. However, even in anterior cancer, in a few patient of there showed high Gleason scores and pT stages at rates cannot be ignored.
3. From 1,344 patients with placental lesions evaluated at our hospital, we extracted data from 21 cases of placental hemangiomas to investigate clinicopathologic features. Placental hemangiomas were more common in women who were primiparas, had multiple births, or had given birth to a girl; and hemangioma size was positively correlated with risks for fetal hydrops and right heart load. Histologic examination showed that most lesions were capillary hemangiomas. One case had features of a lymphangioma or lymphatic malformation.
4. We reviewed clinicopathologic features in 12 cases of malignant mesonephric tumors. Half of these tumors had arisen in the uterine cervix, but other primary sites included the uterine corpus, ovary, and paraovarian structures. Mesonephric remnants or hyperplasia was seen in only 4 patients. Histologic examination often showed a variegated appearance with features resembling endometrioid adenocarcinoma. Some tumors were composed mainly of spindle cells or resembled carcinosarcoma. The histogenesis included tumors derived from mesonephric remnants or hyperplasia, and adenocarcinoma with differentiation into a mesonephric tumor was considered.
5. We examined the histologic features of placental mesenchymal dysplasia at 21 weeks or less of pregnancy. Compared with pregnancy at week 20 and later, characteristic findings included changes resembling a partial hydatid mole and blood vessel proliferation in the villous stroma.
6. Luteinized thecomatosis with sclerosing peritonitis is a rare disease characterized by bilateral ovarian luteinized thecomas and peritonitis. Some authors suggest that these ovarian lesions may be either neoplastic or reactive, but no consensus exists. Whether the ovarian lesions are related to the peritoneal lesions is also unknown. Histologic examination in our case showed proliferation of spindle cells, mixed with some luteinized oval cells, in the ovarian cortex bilaterally. The oval cells had features of a thecoma, but uniform proliferation suggesting a tumor could not be confirmed; therefore, it was also difficult to distinguish between a neoplastic lesion versus a reactive lesion in our patient. In addition, the association between ovarian and omental lesions is unclear.

Other research

1. We performed an autopsy in a case of Chagas disease diagnosed while the patient was still alive. Amastigotes were found in the myocardium and brain. This patient had a history of long-term overseas business trips. Therefore, with the increase of persons born and coming from abroad or returning from abroad to Japan, prophylaxis against Chagas disease should be considered.
2. We encountered a case of angiomatoid fibrous histiocytoma in the left upper arm of a 7-year-old girl. Although this tumor is rare, it was diagnosed on the basis of characteristic clinical and pathological findings. Serum levels of interleukin 6 levels were elevated before surgery but decreased after surgery. Immunohistologic staining showed that the tumor was positive for interleukin.

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