Original Articles

Occurrence of Spontaneous Tumors in the Central Nervous System (CNS) of F344 and SD Rats

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In order to accurately assess the carcinogenicity of chemicals with regard to rare tumors such as rat CNS tumors, sufficient information about spontaneous tumors are very important. This paper presents the data on the type, incidence and detected age of CNS tumors in F344/DuCrI Crlj (a total of 1363 males and 1363 females) and Crl:CD(SD) rats (a total of 1650 males and 1705 females) collected from in-house background data-collection studies and control groups of carcinogenicity studies at our laboratory, together with those previously reported in F344 and SD rats. The present data on F344/DuCrI Crlj rats (F344 rats) and Crl:CD(SD) rats (SD rats) clarified the following. (1) The incidences of all CNS tumors observed in F344 rats were less than 1%. (2) The incidences of malignant astrocytoma and granular cell tumor were higher in male SD rats than in female SD rats. (3) The incidences of astrocytoma and granular cell tumor were higher in SD rats than in F344 rats. (4) Among astrocytoma, oligodendroglioma and granular cell tumor, oligodendroglioma was detected at the youngest age, followed by astrocytoma, and ultimately, granular cell tumor developed in both strains. The incidences observed in our study were almost consistent with those previously reported in F344 and SD rats.

Original Articles

Corneal Mineralization in Wistar Hannover Rats

Satomi HASHIMOTO, Takuya DOI, Yumi WAKO, Junko SATO, Sou WADA, Minoru TSUCHITANI

We have recently started using Wistar Hannover rats in Japan and are now collecting background data. We have been frequently observing corneal mineralization in Wistar Hannover rats of both the RccHan™:WIST and Crl:WI (Han) strains. In this study, details of corneal mineralization in Wistar Hannover rats were histopathologically and ultrastructurally investigated. According to the results, Wistar Hannover rats had a much higher incidence of corneal mineralization compared with Sprague-Dawley rats. The incidence of
corneal mineralization was higher in males than females. According to the histological examination, mineral deposits were positive for calcium by von Kossa’s method. Furthermore, in response to mineralization, keratocytes probably become active to play an important role against the mineralized substance.

Original Articles

**Pulmonary Edema Due to Oral Gavage in a Toxicological Study Related to Aquaporin-1, -4 and -5 Expression**

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A one-time oral gavage can be enough to cause of alveologenic edema with higher expression of AQP-1 and -4 than that with repeated-dose oral gavage, which caused both profound perivascular edema and hydrostatic pressure edema, while AQP-5 was similarly expressed. The alteration of AQPs expression was probably related to alveolar fluid clearance across the alveolar and bronchiolar epithelium in different stages of lung injury. The results clarified the type of lung edema in acute and sub-chronic toxicity studies without treatment related effect of tested material. The pathogenesis of pulmonary edema due to oral gavage toxicological study is associated with the cellular immune response to the reflux materials. Mast cell and leukocyte accumulation may contribute to increase vascular permeability leading to permeability edema. The increase in alveolar septum epithelium, perivascular and peribronchial cuffing, accumulation alveolar lipid containing macrophage and medial hyperplasia of the pulmonary artery might have been caused to increase airway resistance, which resulted in hydrostatic pressure edema.

Original Articles

**Biochemical and Histological Study of Rat Liver and Kidney Injury Induced by Cisplatin**

Sarawoot PALIPOCH, Chuchard PUNSAWAD


Cisplatin is a chemotherapeutic agent widely used in treatment of several cancers. It is documented as a major cause of clinical nephrotoxicity and hepatotoxicity. The purpose of this study was to investigate the involvement of oxidative stress in the pathogenesis of cisplatin-induced liver and kidney injury. Wistar rats were divided into four groups. Group 1 (control) was intraperitoneally (IP) injected with a single dose of 0.85% normal saline. Groups 2, 3 and 4 were IP injected with single doses of cisplatin at 10, 25 and 50
mg/kg body weight (BW), respectively. At 24, 48, 72, 96 and 120 h after injection, BW, levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, malondialdehyde (MDA), and activity of superoxide dismutase (SOD) and histology of the liver and kidney were evaluated. Cisplatin caused a reduction in BW of rats in groups 2, 3 and 4 at all post injection intervals. The levels of serum ALT, AST, BUN and creatinine and MDA of the kidney and liver were markedly increased especially at 48 and 72 h, whereas the activity of SOD was decreased after cisplatin injection. Liver sections revealed moderate to severe congestion with dilation of the hepatic artery, portal vein and bile duct and disorganization of hepatic cords at 50 mg/kg of cisplatin. Kidney sections illustrated mild to moderate tubular necrosis at 25 and 50 mg/kg of cisplatin. Therefore, oxidative stress was implicated in the pathogenesis of liver and kidney injury causing biochemical and histological alterations.

**Case Reports**

**Spontaneous Malignant T Cell Lymphoma in a Young Male Common Marmoset (Callithrix jacchus)**

Itaru YAMAGUCHI, Kensuke MYOJO, Hiroko SANADA, Eri SUDO, Sayaka OOTSUKA, Hiroshi OKUMURA, Atsuko TAKAMI, Tomomi YONESHIGE, Yui SUZUKI, Minami IMAIZUMI, Chie TAKADA, Naoya KIMOTO, Koji SAEKI, Katsumi TAKABA


We histopathologically and immunohistochemically investigated a case of malignant lymphoma that spontaneously developed in a male common marmoset at two years of age. Beginning at two years four months of age, the animal had an enlargement of the submandibular and inguinal lymph nodes, small subcutaneous nodules near the right breast and an approximately fivefold increase in peripheral lymphocyte count compared with the previous examination value. The postmortem findings at two years eight months of age showed lymphadenopathy with enlargement of the thymus and spleen. Small- to intermediate-sized neoplastic lymphocytes had diffusely proliferated in the enlarged nodes. The neoplastic cells were pleomorphic and had irregularly shaped nuclei. The nuclear chromatin staining revealed hyperchromatism in the small-sized cells, and the intermediate-sized cells exhibited vesicular staining. An immunohistochemical examination indicated that the neoplastic lymphocytes were positive for CD3 and negative for CD20, thus suggesting that they had originated from T cells. In addition, the proliferation of high endothelial venules and reactive epithelioid histiocytes was observed. Scattered tingible body-laden macrophages were infrequently detected. Neoplastic lymphocytes were also observed in the thymus, spleen, heart, lungs, liver, kidneys, adrenal glands and femoral and sternal bone marrow. This malignant lymphoma in a young male common marmoset was considered to fit the category of “peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)” according to the new WHO system of classification.
Case Reports

Spontaneous Extraskeletal Osteosarcoma in a Rabbit (*Oryctolagus cuniculus*): Histopathological and Immunohistochemical Findings

Kavindra Kumara WIJESUNDERA, Takeshi IZAWA, Daisuke FUJITA, Yuki DENDA, Eiko SETO, Sasai HIROSHI, Mitsuru KUWAMURA, Jyoji YAMATE


A spontaneously occurring subcutaneous mass in the left forelimb of a nine-year-old rabbit (*Oryctolagus cuniculus*) was examined histopathologically and immunohistochemically. Clinically, edema and hemorrhage were seen around the mass. No connection of the tumor mass to the appendicular skeleton was found. The tumor was arranged in a solid growth pattern and irregular bundles, and neoplastic cells were polygonal to spindle-shape. Osteoid (positive for osteocalcin) and multinucleated giant cells were diffusely or focally seen. Neoplastic cells were positive for vimentin, osterix and Ki-67, indicating the nature of osteoblasts with proliferating activity, but negative for α-smooth muscle actin, desmin or CD204. Based on these findings, a diagnosis of extraskeletal osteosarcoma was made, a very rare tumor both in laboratory and pet rabbits.

Case Reports

Bacterial Pleuritis with Thickened Mesothelial Hyperplasia in a Young Beagle Dog

Naoaki YAMADA, Satomi HASHIMOTO, Yuki TOMONARI, Hiroko KOKOSHIMA, Takuya DOI, Junko SATO, Yumi WAKO, Minoru TSUCHITANI


A five-month-old male beagle dog suddenly became moribund. Bloody fluid accumulated in the thoracic and abdominal cavities, and soft yellow flecks were floating in the thoracic fluid. The mediastinum and pericardium became dark reddish with villous thickening. Other parietal and pulmonary pleurae were rough, and the organs adhered to each other. Histologically, most mediastinal pleura formed papillary projections covered by a single layer of mesothelial cells. Many macrophages and neutrophils infiltrated the submesothelial connective tissue. At the mediastinum adjacent to the pericardium, cuboidal mesothelial cells proliferated solidly and formed a thick surface stratum. The flecks consisted of gram-negative filamentous or small bacillary (coccoid) bacteria. In the right posterior lobe of the lung, neutrophilic infiltration and a large encapsulated abscess including a bacterial colony were present. We diagnosed this...
case as “bacterial pleuritis with thickened mesothelial hyperplasia”. The cause of the pleuritis might be a chronic pleural infection spread via the lung abscess.

Case Reports
A Case of Metastatic Adrenocortical Carcinoma Diagnosed with Steroidogenic Factor-1 in a Sprague-Dawley Rat
Yuichi TAKAI, Tomoya SANO, Takeshi WATANABE, Ryo FUKUDA


This report describes the morphological and immunohistochemical characteristics of an adrenocortical carcinoma with distant metastasis in a Sprague-Dawley rat. Macroscopically, a single large mass was observed in the adrenal gland, and multiple nodules were noted in the lung, liver, and thyroid. Histologically, the adrenal tumor consisted of a solid growth of eosinophilic round cells with nuclear atypia. Vascular invasion was present, and multiple metastatic lesions were also observed in the lungs, liver, and mediastinal lymph nodes. Immunohistochemically, the nuclei of these tumor cells were positive for Steroidogenic Factor-1 (SF-1). In the thyroid, tumor cells histologically resembling adrenal cells were immunohistochemically negative for SF-1 but positive for calcitonin; thus the lesion was diagnosed as thyroid C-cell carcinoma. From these results, the present case was diagnosed as adrenocortical carcinoma with distant metastases. SF-1 could be a valuable marker for the differential diagnosis of adrenocortical tumors versus other endocrine tumors such as C-cell carcinoma.

Case Reports
Spontaneous Ameloblastic Fibroma in a Young Guinea Pig
Makoto TANAKA, Osamu SAWAMOTO


A spontaneous ameloblastic fibroma was found in a 9-week-old guinea pig. Histopathologically, neoplastic cells consisted of two components: an odontogenic epithelium and odontogenic mesenchyme. The odontogenic epithelium formed strands, nests, and islands that were interspersed within the odontogenic mesenchyme. In the marginal region, odontoblasts and scant dysplastic eosinophilic material were seen between these two components. Immunohistochemically, the odontogenic epithelium was positive for cytokeratin AE1/AE3, and the odontogenic mesenchyme and odontoblast were positive for vimentin, in the same manner as in the normal tooth germ (control). We could not obtain conclusive data suggesting that the eosinophilic material was dental hard tissue because the eosinophilic material was not stained.
specifically by any methods. Based on these histological characteristics, the tumor in the present case was diagnosed as an ameloblastic fibroma. This is the first report of ameloblastic fibroma in guinea pigs.

Short Communication

Testicular Mineralization in KK-A\textsuperscript{y} Mice Treated with an Oxovanadium Complex

Takayasu MOROKI, Yutaka YOSHIKAWA, Katsuhiko YOSHIZAWA, Airo TSUBURA, Hiroyuki YASUI


Vanadium has potential for use in diabetes therapy. Many investigators have reported toxic effects of inorganic vanadium salts; however, there are few reports on toxic effects of oxovanadium(VO\textsuperscript{2+}) complexes. Therefore, we studied VO\textsuperscript{2+} toxicity by examining histological changes and measuring the vanadium concentration in the testis after repeated oral administration of bis(1-oxy-2-pyridine-thiolato)oxovanadium(VO\textsuperscript{2+}) (VO(opt)\textsubscript{2}) for 2 or 4 weeks in KK-A\textsuperscript{y} mice. Severe mineralization and degeneration/necrosis of the seminiferous tubules were detected after either 2 or 4 weeks of administration. Vacuolar changes in Sertoli cells and the seminiferous epithelia, and hyperplasia of Leydig cells were observed in the testes of some animals. Vanadium concentrations in the mineralized testis were much higher than those in the testis of untreated KK-A\textsuperscript{y} mice. These results represent the first report of the possibility for seminiferous tubules mineralization induced by VO(opt)\textsubscript{2} administration. Therefore, our research provides important information about the potentially toxic effects of VO\textsuperscript{2+} complexes.