A Retrospective Histopathological Survey on Canine and Feline Liver Diseases at the University of Tokyo between 2006 and 2012

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ABSTRACT. To determine the incidence of hepatic diseases in dogs and cats in Japan, a retrospective study was performed using data of 463 canine and 71 feline liver biopsies at the Veterinary Medical Center of the University of Tokyo. The most common canine hepatic disease was microvascular dysplasia (MVD) and occupied 29.4% of all diagnoses. This terminology might contain “real” MVD and primary portal vein hypoplasia, because these two conditions were difficult to be clearly distinguished histopathologically. Parenchymal and interstitial hepatitis and primary hepatic tumors accounted for 23.5% and 21.0% of the diagnoses, respectively. Parenchymal and interstitial hepatitis occupied 34.1% of non-proliferative canine hepatic diseases, while hepatocellular adenoma and carcinoma were 26.6% and 24.5% of proliferative hepatic diseases, respectively. Breed-specificity was seen in MVD for Yorkshire terrier, Papillon and Toy poodle, in hepatitis for Doberman pinscher and Labrador retriever, in cholangiohepatitis for American cocker spaniel, Miniature schnauzer and Pomeranian, in hepatocellular adenoma for Golden retriever and Shiba and in hepatocellular carcinoma for Shih Tzu. The most common feline liver disease was parenchymal and interstitial hepatitis (45.1% of all diagnoses). Among feline hepatitis, neutrophilic cholangiohepatitis (23.9%), lymphocytic cholangiohepatitis (14.1%) and chronic hepatitis (5.6%) were recorded. Adult polycystic liver disease was 5.6%. Among proliferative diseases in the feline liver (11.3% of the all), lymphoma (4.2%) and primary epithelial tumors (4.2%) including hepatocellular carcinoma, cholangiocellular adenoma and cholangiocellular carcinoma were observed. Hepatic degeneration was 14.1%, and MVD was 12.7%, respectively.

KEYWORDS: canine, epidemiology, feline, liver disease, pathology.

The aim of the present study is to reveal the incidence of hepatic diseases in dogs and cats in Tokyo area, Japan, through histopathological data.

MATERIALS AND METHODS

The pathological database at the Department of Veterinary Pathology, the University of Tokyo (UT) was used in the present study. The database consists of basic data of patients (age, breed and gender), clinical information and histopathological features of biopsy cases sampled at the Veterinary Medical Center (VMC) at UT. We searched the database using key words of “liver biopsy” or “liver”. Totally, 4,755 cases of dogs and 1,016 cases of cats were chosen, which had been biopsied during 6 years and 2 months, between November 2006 and December 2012.

Of the 4,755 cases of dogs and of 1,016 cases of cats, 463 and 71 were hepatic diseases, respectively. Among them, 414 and 68 cases were histopathologically available, respectively. These cases were reviewed histologically according to the WSAVA’s criteria by the pathologists. If there had been more than two diagnoses for one case, only a main diagnosis could be adopted. The diagnoses were basically based on the WSAVA criteria, but we adopted other diagnoses not within the criteria: the diagnosis “MVD” in the present study included primary portal vein hypoplasia, because these two diagnoses are difficult to be distinguished.
RESULTS

Canine liver biopsies: Of 4,755 canine biopsy cases, 463 (9.7%) were liver biopsies, including 320 (69.1%) non-proliferative and 139 (30.0%) proliferative liver diseases. In the remaining 4 cases, there were no significant lesions. The results are summarized in Tables 1–4.

Canine non-proliferative liver diseases: MVD occupied 42.5% (136 of 320) of non-proliferative diseases. The ratio of MVD with PSS was 87.0% (114 of 131), and that without PSS was 13.0% (17 of 131). The data on PSS of the other 5 MVD cases were not available. Parenchymal and/or interstitial hepatitis accounted for 34.1% (109 of 320, 23.5% of all diagnoses), being the second popular non-proliferative liver disease in the dog. Parenchymal hepatitis included canine chronic hepatitis (22.9%, 25 of 109) and liver fibrosis (11.9%, 13 of 109), and interstitial hepatitis included cholangiohepatitis (55.0%, 60 of 109) and cholangitis (7.3%, 8 of 109). The hepatitis mentioned above was all chronic hepatitis. The third most often encountered liver disease was hepatic degeneration (15.3%, 49 of 320).

Each major non-proliferative disease had a breed-specific tendency. Among 136 cases of MVD, Yorkshire terriers ranked first (27 cases, 19.9%), toy poodles second (16 cases, 11.8%) and papillons third (13 cases, 9.6%). Female Yorkshire terriers were more susceptible than male ones (male/female=9:18), while males were more susceptible in toy poodles and papillons (male/female=11:5 and 12:1, respectively). The median age of MVD was 1 year and 9 months old, and the mean age was 3 years and 2 months old.

Among 60 cases of cholangiohepatitis, miniature dachshunds ranked the first (11 cases, 18.3%), and American cocker spaniels (5 cases, 8.3%) and Shih Tzu ranked second (5 cases, 8.3%) and papillons third (5 cases, 8.3%) second. Male miniature dachshunds were more susceptible than females (male/female=9:2). The median age of the disease was 9 years and 7 months old.

Among 25 cases of canine chronic hepatitis, Labrador retrievers and Doberman Pinschers ranked the first (8 cases, 32.0%) and the second (3 cases, 12.0%), respectively. Females were more susceptible than males in both breeds [Labrador retrievers (male/female=1:7) and Doberman pinchers (male/female=1:2)]. The median age of the hepatitis cases was 8 years and 7 months old. Eight of the 25 canine chronic hepatitis cases had copper deposition. Two of the 8 cases were Doberman pinchers, and 1 was Labrador retriever, Bedlington terrier, Welsh corgi, Cavalier King Charles spaniel or a mixed breed.

Canine proliferative liver diseases: Of 139 cases of canine proliferative liver diseases, primary epithelial tumors were 74 cases (53.2%, including hepatocellular adenoma (26.6%) and hepatocellular carcinoma (24.5%)), followed by nodular hyperplasia (26 cases, 18.7%), primary non-epithelial tumors (23 cases, 16.5%) and metastatic tumors (16 cases, 11.5%). That is, primary hepatic tumors were 97 cases (21.0% of the all). Among the 113 neoplastic cases excluding nodular hyperplasia, hepatocellular adenoma was in the first place (37 cases, 32.7%) and hepatocellular carcinoma in the second (34 cases, 30.1%). There was no breed predilection in nodular hyperplasia. The median age of the lesion was 11 years and 9 months old, and no sex difference in the occurrence was observed. As for hepatocellular adenoma, Golden retrievers, Shihbas and mixed breeds were of the highest incidence (13.5%, 5 of 37), respectively. The median age was 12 years and 1 month old, and there was no sex differences in each breed (16:21). In hepatocellular carcinoma, Shih Tzu was the breed of the highest incidence.
followed by Yorkshire terriers (11.8%, 4 of 34). The median age was 11 years and 6 months old, and no sex difference was observed. **Feline liver biopsies:** Of 1,016 feline biopsy cases, 71 (7.0%) were liver biopsies. In the data, non-proliferative liver diseases were 56 (78.9% of all diagnoses), and proliferative diseases were 8 (11.3% of the all). In the remaining 7 cases, there were no significant lesions. The results are summarized in Tables 5–7.

### Feline non-proliferative liver diseases

Parenchymal and interstitial hepatitis occupied 57.1% (32 of 56) of non-proliferative liver diseases (45.1% of the all diagnoses), including neutrophilic cholangiohepatitis (53.1%, 23.9% of the all), lymphocytic cholangiohepatitis (31.3%, 14.1% of the all), chronic hepatitis (12.5%, 5.6% of the all) and neutrophilic cholangitis (3.1%, 1.4% of the all). There was one case of giant cell hepatitis. Copper deposition in chronic hepatitis and in cholangiohepatitis was seen in one case, respectively. The second popular non-proliferative liver disease was hepatic degeneration (17.9%, 10 of 56, 14.1% of the all), including 3 cases of lipidosis. The third most often encountered disease was MVD (16.1%, 9 of 56, 12.7% of the all). The fourth was adult polycystic liver disease (7.1%, 4 of 56, 5.6% of the all). One of the 4 cases was accompanied with polycystic kidney disease.

| Diagnosis                  | Number of cases |
|----------------------------|-----------------|
| Primary epithelial tumors  |                 |
| Hepatocellular carcinoma   | 34              |
| Hepatocellular adenoma      | 37              |
| Cholangiocellular carcinoma| 2               |
| Cholangiofibrolastic adenoma| 1              |
| Primary nonepithelial tumors|              |
| Carcinoid tumor             | 5               |
| Lymphoma                   | 5               |
| Sarcoma (not otherwise specified) | 5      |
| Hemangiosarcoma             | 4               |
| Malignant peripheral nerve sheath tumor | 1 |
| Lymphangiosarcoma           | 1               |
| Fibrosarcoma                | 1               |
| Histiocytic sarcoma         | 1               |
| Metastatic tumors           |                 |
| Hemangiosarcoma             | 3               |
| Mammary gland carcinoma     | 3               |
| Lymphoma                   | 2               |
| Sarcoma (not otherwise specified) | 2      |
| Gastrointestinal stromal tumor | 1  |
| Mast cell tumor             | 1               |
| Islet cell adenocarcinoma   | 1               |
| Lung adenocarcinoma         | 1               |
| Peripheral nerve sheath tumor | 1  |
| Smooth muscle sarcoma       | 1               |
| Other proliferative diseases|                 |
| Nodular hyperplasia         | 26              |

| Diagnosis                | Number of cases |
|--------------------------|-----------------|
| Dog breeds, median age and male-to-female ratio of non-proliferative liver diseases in dogs |
|                          | Number of cases |
|                          |                 |
| **Table 2.** Breed, median age and male-to-female ratio of non-proliferative liver diseases in dogs |
| Diagnosis                | Breed           | Nm | Median age | Male:female | % a) | % b) | P value c) | OR | 95% CI of OR |
| Cholangiohepatitis       | Miniature Dachshund | 60 | 9 y 7 m   | 28:32       | 35.3% | 12 of 34 | 1017         |
|                          | American Cocker Spaniel | 11 | 10 y 9 m  | 28:32       | 35.3% | 12 of 34 | 1017         |
|                          | Yorkshire Terrier | 11 | 10 y 9 m  | 28:32       | 35.3% | 12 of 34 | 1017         |
|                          | Toy Poodle       | 11 | 10 y 9 m  | 28:32       | 35.3% | 12 of 34 | 1017         |
|                          | Papillon         | 11 | 10 y 9 m  | 28:32       | 35.3% | 12 of 34 | 1017         |
|                          | Other proliferative diseases | 26 |           |               |        |        |              |

Nm, number of cases; OR, odds ratio; CI, confidence interval; ND, no data available; y, year (s); m, month (s). a) The number of cases of a breed / the total number of cases of the diagnosis X 100. b) The number of cases of a breed / the total number of cases of the breed including all breeds X 100. c) P value from the χ² test between % of a breed in total liver biopsy samples and % of the breed in total biopsy samples.
months, and the male/female ratio was 1:3.

**Feline proliferative liver diseases**: The most popular proliferative liver disease was lymphoma (37.5%, 3 of 8, 4.2% of the all). Hepatocellular carcinoma, cystic cholangiocellular adenoma and cholangiocellular carcinoma were 12.5% (1 of 8), respectively. That is, primary epithelial tumors were 4.2% of the all.

The median age of lymphoma was 11 years and 9 months old, and all of the cases were female.

**DISCUSSION**

The present study was the first incidence survey on canine and feline liver diseases in Japan. We demonstrated here that the most popular canine liver disease was MVD (29.4%), followed by hepatitis (23.5%) including cholangiohepatitis and cholangitis and by primary hepatic tumors (21.0%) including hepatocellular carcinoma and adenoma. We propose that the term of “MVD” is more appropriate rather than “primary portal vein hypoplasia”, which is used in the WSAVA’s criteria, to represent the lesion histopathologically, because the lesion includes not only hypoplasia of the portal vein but also microvascular proliferation.

Labrador retrievers, American Cocker spaniels and Doberman pinschers were known to be the breeds prone to chronic hepatitis [3]. There were histological differences among hepatitis of these three breeds. The hepatitis in Labrador retrievers was characterized by severe infiltration of inflammatory cells into the parenchyma. That of American Cocker spaniels was by less infiltration of inflammatory cells and severer liver fibrosis. Besides, the hepatitis of Doberman pinschers was often characterized by severe copper deposition. The result of the present study partly supported the previous description [3].

According to the reports by Patnaik et al. [23, 24], the incidence of hepatocellular carcinoma was 52% of total primary hepatic neoplasms. The mean age of hepatocellular carcinoma was 11 years old. There was a male predominance (male/female=1.7:1) and no breed predisposition. In the present study, the incidence of hepatocellular carcinoma was 35.1% of total primary hepatic neoplasms. The mean age was 13 years and 1 month old in the present study. There was no sex predisposition, whereas Shih Tzu was the breed with highest incidence. The ratio of hepatocellular carcinoma versus hepatocellular adenoma was approximately equal (34:37), indicating no predominant incidence between malignant and benign tumors. These results were inconsistent with the previous study in the United States [21], reflecting the difference in a breed-popularity between Japan and the United States. The ratio of nodular hyperplasia to total proliferative hepatic diseases was 18.7% in the present study. This indicated that approximately one-fifth of hepatic masses sampled from patients through biopsy were with completely benign prognosis, because nodular hyperplasia neither causes any significant hepatic dysfunctions nor expresses any clinical symptoms.

The present survey showed that the most popular canine

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### Table 4. Breed, median age and male-to-female ratio of neoplastic liver diseases in dogs

| Diagnosis                  | Breed          | Nm  | Median age | Male:female | % a)  | % b)  | P value c)      | OR   | 95% CI of OR |
|----------------------------|----------------|-----|------------|-------------|-------|-------|-----------------|------|--------------|
| Hepatocellular carcinoma   | Shih Tzu       | 34  | 11 y 6 m   | 14:20       | 0.001 | 7.58  | <0.001         | 8.89 | 4.38–18.02   |
|                            | Yorkshire Terrier | 4  | 12 y 1 m   | 2:2         | 0.001 | 7.58  | <0.001         | 2.85 | 1.00–8.11    |
|                            | Golden Retriever | 5  | 12 y 1 m   | 2:2         | 0.001 | 7.58  | <0.001         | 3.92 | 1.52–10.09   |
|                            | Mixed-breed    | 5   | 12 y 1 m   | 2:2         | 0.001 | 7.58  | <0.001         | 4.63 | 1.80–11.95   |

Nm, number of cases; OR, odds ratio; CI, confidence interval; ND, no data available; y, year (s); m, month (s). a) The number of cases of a breed / the total number of cases with the diagnosis X 100. b) The number of cases of a breed / the total number of cases of the breed including all breeds X 100. c) P value from the χ² test between % of a breed in total liver biopsy samples and % of the breed in total biopsy samples.

### Table 5. Incidence of non-proliferative liver diseases in cats

| Diagnosis                      | Number of cases |
|--------------------------------|-----------------|
| Inflammatory responses         |                 |
| Neutrophilic cholangiohepatitis | 17              |
| Lymphocytic cholangiohepatitis  | 10              |
| Neutrophilic cholangitis        | 1               |
| Chronic hepatitis               | 4               |
| Regressive changes              |                 |
| Hepatic degeneration            | 10              |
| Microvascular dysplasia         | 9               |
| Biliary disorders               |                 |
| Adult polycystic liver disease  | 4               |
| Others                          |                 |
| Anomalous artery                | 1               |

### Table 6. Incidence of proliferative liver diseases in cats

| Diagnosis                      | Number of cases |
|--------------------------------|-----------------|
| Primary epithelial tumors      |                 |
| Hepatocellular carcinoma       | 1               |
| Cystic cholangiocellular adenoma| 1               |
| Cholangiocellular carcinoma    | 1               |
| Primary nonepithelial tumors   |                 |
| Lymphoma                       | 3               |
| Plasmacytoma                    | 1               |
| Sarcoma (not otherwise specified) | 1           |
hepatic disease in Japan was neutrophilic cholangiohepatitis (23.9%, 17 of 71). The second ones were lymphocytic cholangiohepatitis and hepatic degeneration including lipodosis (each 14.1%, 10 of 71), respectively. MVD, the most popular canine liver disease in Japan, was the fourth (12.7%, 9 of 71). The present results showed that neutrophilic cholangiohepatitis was a disease of older cats in comparison with lymphocytic cholangiohepatitis, consistent with those of previous reports in other countries [16, 20, 26]. Neutrophilic cholangiohepatitis in the chronic stage was associated with the infiltration of mixed inflammatory cells consisting of neutrophils, lymphocytes and plasma cells [19]. However, neutrophilic cholangiohepatitis can be distinguished from lymphocytic cholangiohepatitis that is often characterized by distinct lymphoid follicle formation around the bile ducts and/or portal areas.

Hepatic copper deposition was reported in a European shorthair cat with chronic hepatitis and cirrhosis [22] and in a Siamese cat with hepatopathy [15]. In the present survey, two Japanese domestic cats with chronic hepatitis and neutrophilic cholangiohepatitis had moderate hepatic copper deposition. Although hepatic lipodosis is one of the most common liver diseases in cats in North America [2, 8, 12, 14, 30], it occupied only 4.2% (3 of 71) of liver diseases in Japan. The difference in the prevalence of feline hepatic lipodosis between Japan and North America might reflect the difference in breeds kept or foods.

We propose that “MVD” is more suitable than “primary portal vein hypoplasia” also for feline cases, because the lesion includes not only portal vein hypoplasia but also microvascular proliferation as in canine cases. MVD in cats has been seldom reported up to the present [17]. In the present study, however, the disease accounted for 12.7% (9 of 71) of liver diseases. The ratio of MVD with PSS in cats was less than that in dogs both in the present result and a previous report [27]. This may indicate that cats are less susceptible to PSS than dogs [4, 27].

In Japan, feline adult polycystic liver disease was 5.6% (4 of 71). Among 4 cases of adult polycystic liver disease, a case was accompanied with polycystic kidney disease; consistent with a previous report [6] in which cats with single- or multiple-cysts in the liver also had polycystic kidney disease. As for proliferative diseases, the number of primary epithelial tumors was less than that of primary nonepithelial tumors, and the most common neoplasm was lymphoma (4.2%, 3 of 71). In the present study, lymphoma accounted for 37.5% of feline hepatic tumors (n=8). This is consistent with the results of a previous report [9]; the incidence of feline lymphoma was higher than that of other malignant hepatic neoplasms.

There is, however, a limitation and a bias in this study, because the sampling itself is strongly influenced by some clinical matters, such as the difficulty of biopsy, according to the balance between advantages and disadvantages. If a diagnosis can be obtained by other imaging devices, such as CT and MRI, liver biopsy is not always needed. However, there have been no incidence surveys of canine and feline liver diseases previously in Japan. The present data will be a reference standard for histopathological studies of liver diseases.

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