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## Biliary Cystadenoma of Cats

R. ADLER AND D. W. WILSON

**Abstract.** Published surveys of feline neoplasia have not specifically included biliary cystadenoma, and there is only one case report in the literature. This report is a compilation of 13 feline cases and provides a description of clinical, pathologic, immunohistochemical, and ultrastructural aspects of biliary cystadenoma as well as a discussion of comparative pathology of biliary cystadenoma in human beings and speculative histogenesis.

*Key words:* Biliary cystadenoma; cats; liver.

Biliary cystadenoma is a rare neoplasm of humans<sup>6</sup> and animals<sup>17</sup> that arises in the liver and less often in the extrahepatic bile ducts. The neoplasm is characterized by focal or multicentric cystic proliferation of biliary epithelium involving one or more hepatic lobes. Surveys of feline neoplasms do not include this unusual neoplasm.<sup>5,13,18,20</sup> In this report, we describe clinical, pathologic, immunohistochemical, and ultrastructural aspects of biliary cystadenoma as seen in 13 domestic cats and provide comparisons with the same entity in human beings.

Pathology submissions (biopsy and necropsy) of domestic cats to the Veterinary Medical Teaching Hospital of the University of California at Davis were searched from 1973 to 1990 for cases diagnosed as any form of biliary growth. Archived slides were reviewed. Excluded were individual cases diagnosed as bile duct cysts, solitary retention cyst, intrahepatic biliary cyst, bile duct hamartoma, noncystic bile duct adenoma, and two cases of biliary cystadenoma in exotic cats (mountain lion and panther). Two cases were reclassified as cystadenoma; one was previously called proliferative cystic biliary anomaly, and the other was classified as bile duct adenoma without cystic modifier. Summaries for those cases histologically confirmed as cystadenoma are shown in Table 1. The average age of the affected cats was 14.5 years (range, 12–17 years); there was no sex prevalence in these 13 cases. A palpable abdominal mass was the major clinical sign in six cats (Nos. 1–6). Two cats were icteric (Nos. 7, 8), but this was not attributable to biliary cystadenoma in either case; cat No. 7 had xenobiotic-induced hepatocellular disease, and cat No. 8 had obstructive cholecystitis. In the remaining cats, the neoplasms were incidental findings at necropsy or laparotomy. The majority of clinically apparent neoplasms were multicentric, whereas incidental neoplasms were usually focal.

The typical gross appearance of the neoplasm is shown in Fig. 1. One or more hepatic lobes contained multilocular thin-walled cysts that expanded beyond the capsular surface. Cysts were filled with clear, watery to slightly viscous fluid and varied in diameter from 2 to 15 mm. Neither extrahepatic bile duct involvement nor metastases were found in any case.

Histologically, these neoplasms replaced and compressed extensive portions of the hepatic parenchyma with coalescing thin-walled cysts of various sizes. The cyst lining (Fig. 2) consisted of mature simple cuboidal or attenuated epithelium with occasional papillary formation. Epithelial cells showed no atypia and had small round to oval vesicular nuclei with

granular chromatin, rare nucleoli and mitotic figures, and homogeneous cytoplasm. These cells covered narrow bands of moderately cellular fibrovascular stroma. Mature smooth muscle fibers and inflammatory cells were found occasionally within the stroma. Frequently, there were entrapped islands of hepatocytes in the interstitium. The proteinaceous fluid within cysts stained positively with periodic acid–Schiff stain. Hyperplastic bile ducts were occasionally present at the periphery of the neoplasm (cat Nos. 1, 3, 5, 6, 8). Some of the neoplasm-laden hepatic lobules also had lymphocytic cholangitis or cholangiohepatitis (cat Nos. 4, 5, 8), hepatocellular bile pigmentation (cat Nos. 4, 10), hepatic lipidosis and portal fibrosis (cat No. 6), or centrilobular fibrosis and nodular regeneration (cat No. 1). Although lipofuscin-laden macrophages and cyst ulceration are commonly seen in human cystadenomas,<sup>6</sup> only the macrophages were seen among these cats (No. 6).

Trypsinized paraffin sections of neoplasm from six cats (Nos. 6, 8–12) were immunostained using a 1:100 dilution of antibody to cytokeratin Nos. 8, 18, and 19 (52, 45, and 40 kd, respectively) (PKK1, Labsystems Inc., Chicago, IL), the avidin–biotin complex method (Vectastain Kit, Vector Labs, Burlingame, CA), and diaminobenzidine (Sigma Chemical Co., St Louis, MO). We have previously found this method to stain biliary epithelium but not hepatocytes or nonparenchymal cells. In all cases, the epithelial cells lining cysts had a positive immunostaining reaction similar to that seen with normal biliary epithelium.

Formalin-fixed neoplastic tissue with typical histologic features from cat No. 1 was prepared for electron microscopy by dehydrating 1–2-mm osmium-postfixed tissue blocks in a graded series of alcohol and propylene oxide and embedding in Epon–Aryldite plastic. Ultrathin sections stained with lead citrate and uranyl acetate were viewed on a Zeiss EM10 transmission electron microscope. Ultrastructurally, the epithelial cells covering cyst walls had microvilli, apical adhesion zones, and complex interdigitating membranes between cells. They were attached to the cyst wall by a thin basal lamina (Fig. 3). This electron microscopic appearance is typical for biliary epithelium.<sup>7</sup>

Biliary cystadenoma in domestic cats is similar in clinical presentation, behavior, and morphology to the human entity. In human beings, this neoplasm is uncommon, apparently grows slowly, and is seen most often in women >40 years of age.<sup>6</sup> The major presenting signs include upper abdominal pain, persisting for years in some cases, and an abdominal mass. Icterus is rare. The cystic mass or multicentric masses

**Table 1.** Case summaries of 13 domestic cats with biliary cystadenoma.

Cat No.	Age (years)	Sex*	Breed†	Clinical Problems	Neoplasm Distribution
1	17	Mc	DSH	Palpable abdominal mass	Focal
2	13	Mc	SPc	Palpable abdominal mass	Not determined
3	14	Fs	DLH	Palpable abdominal mass	Multicentric
4	15	Fs	DLH	Palpable abdominal mass; hyperthyroidism	Multicentric
5	14	Mc	DSH	Palpable abdominal mass; hyperthyroidism	Multicentric
6	16	Mc	DSH	Palpable abdominal mass; hyperthyroidism	Multicentric
7	13	Mc	DSH	Icterus; neoplasm identified at laparotomy	Focal
8	17	Mc	DSH	Mass incidental at necropsy; obstructive cholecystitis; icterus; hyperthyroidism	Multicentric
9	13	Mc	DLH	Mass incidental at laparotomy; intestinal lymphosarcoma	Multicentric
10	Adult	Fs	DLH	Mass incidental at necropsy; pyelonephritis	Focal
11	14	Mc	DSH	Mass incidental at necropsy; metastatic pulmonary carcinoma	Focal
12	12	Fs	DSH	Mass incidental at necropsy; orbital sarcoma	Focal
13	16	Mc	DLH	Mass incidental at necropsy; multicentric fibrosarcoma	Focal

\* Mc = castrated male; Fs = spayed female.

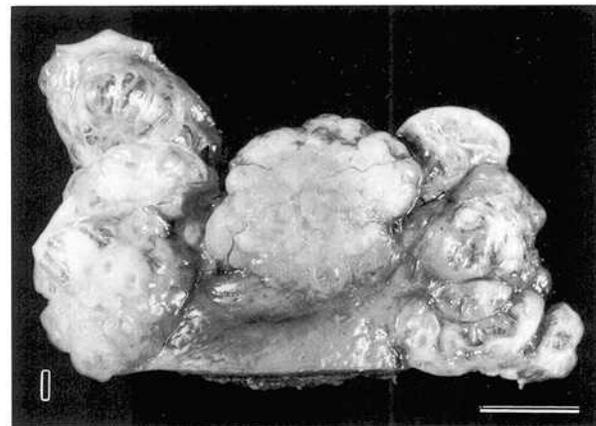
† DSH = Domestic Short Hair; SPc = Siamese-Persian cross; DLH = Domestic Long Hair.

are usually detected by palpation, ultrasonography, radiography, or tomography.<sup>9</sup> Rarely, the neoplasm is discovered at cholecystectomy or autopsy as an incidental finding.<sup>9</sup> As in domestic cats, pathologic evaluation is essential to distinguish biliary cystadenoma from other processes. Needle aspiration and fluid cytology are generally not diagnostic; however, in human cases, assay of carcinoembryonic antigen levels in cyst fluid may distinguish cysts from cystic neoplasms.<sup>15</sup> Mucin and immunohistochemical staining may be helpful in the differential diagnosis of small biopsy specimens from human cases.<sup>22</sup>

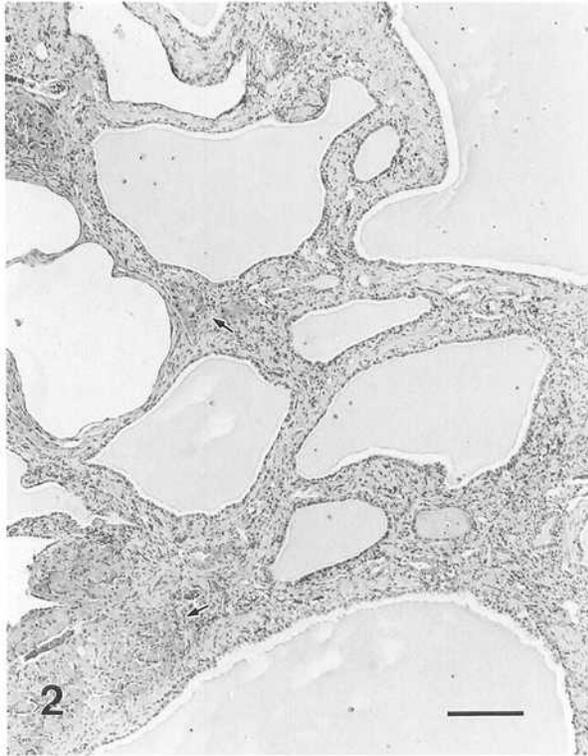
In both human beings and cats, cystadenoma is distinct from other biliary growths such as biliary cysts, noncystic adenomas, cystadenocarcinoma, and cholangiocellular carcinoma. Solitary biliary cysts may enlarge to several centimeters<sup>2,12</sup> but are more often an incidental necropsy finding that lack the extent of hepatic parenchymal involvement and the multilocular complexity of cystadenoma.<sup>23</sup> Another distinguishing feature may be the character of the cystic fluid; retention cysts may contain bile, whereas those containing clear or mucinous fluid are probably neoplastic.<sup>8</sup> Noncystic bile duct adenomas are usually well-circumscribed small solitary nodules,<sup>16</sup> in contrast to multicentric benign growths of cystadenomas; either may be confused with metastases at laparotomy. Similar to cystadenomas, cholangiocellular carcinomas can be multicentric, but in cats they are typically solid umbilicated lesions that often transplant to serosal surfaces.<sup>8</sup> Histologic features that distinguish cystadenocarci-

noma from cystadenoma in human beings include multilayered lining epithelium with numerous papillary projections, cellular atypia, stromal invasion, desmoplasia, and metastasis or transplantation.<sup>6,9</sup>

These cases of feline biliary cystadenoma also appear to be distinct from polycystic disease of the kidney and liver as described in cats,<sup>1,21</sup> dogs,<sup>11</sup> and human beings.<sup>19</sup> Twelve of



**Fig. 1.** Liver; cat No. 1. Gross appearance of liver section with biliary cystadenoma. Note the presence of multilocular thin-walled cysts raised above the capsular surface. Bar = 1 cm.



**Fig. 2.** Biliary cystadenoma; cat No. 1. Note the multicellular complexity of the neoplasm and islands of hepatocytes entrapped within the stroma (arrows). HE. Bar = 150  $\mu$ m.

13 cats in this series had renal evaluation either at necropsy or by laparotomy; none of these had evidence of cystic renal disease.

The source of the neoplasm in both human beings and animals is undetermined;<sup>4</sup> however, congenital and developmental origins have been given most consideration.<sup>2,3,6</sup> Embryonically, there is excessive production of bile ducts, some of which are discontinuous with the biliary tree. Retention cysts arising in these segmentally separated ducts normally involute, but some can persist as biliary microhamartomas or congenital cysts, which may give rise to this neoplasm. Acquired origins have also been shown experimentally.<sup>2,4</sup>

In human beings, the prognosis following neoplasm resection is favorable because metastasis is not a feature<sup>6,10</sup> and recurrence of intrahepatic neoplasms is rare.<sup>23</sup> Complete surgical excision is recommended early because there is concern for malignant transformation to cystadenocarcinoma.<sup>2,6</sup> Cystadenocarcinoma was not found in any of the cats in this series; however, two cats had other biliary malignancies. In cat No. 4, both cystadenoma and cholangiocarcinoma were found in the liver, although in separate lobes. In cat No. 8, bile duct carcinoma was diagnosed in atypical biliary hyperplastic proliferations in the hilus associated with obstructive cholecystitis. This was also separated from the benign cystadenoma. Nonetheless, there may be a biologic spectrum

of cystic biliary neoplasia in cats that includes malignant transformation, as has been discussed for human beings.<sup>2</sup>

Only one cat in this series (No. 1) underwent hepatic resection. This cat survived for more than 2.5 years without recurrence following the removal of 160 g of neoplasm-laden liver tissue. In a single case report,<sup>14</sup> a 15-year-old castrated male domestic short-haired cat was normal 18 months after neoplasm resection. Complete surgical excision should be considered in appropriate cases.

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**Fig. 3.** Electronmicrograph. Epithelium, biliary cystadenoma; cat No. 1. Microvilli, apical adhesion zone, interdigitating membranes, and thin basal lamina typical of biliary epithelium are present. Lead citrate and uranyl acetate. Bar = 0.2  $\mu$ m.

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