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Case Reports

CHOLANGIOCARCIOMA IN A CAT

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SUMMARY

A 7-year-old, intact female Domestic Shorthair cat was referred to University Veterinary Hospital (UVH), UPM for diagnostic workup of a hepatomegaly observed on abdominal radiographs. Physical examination revealed no significant findings except for a distended abdomen. Hematology and serum biochemistry findings included a regenerative anaemia, left shift neutrophilia and a 10-fold elevation in gamma-glutamyltranspeptidase (GGT). Abdominal ultrasound revealed heterechoic liver lobes with irregular margins and presence of nodular and cyst-like structures predominantly affecting the left lobes. A mild ascites was also noted. A fine needle aspiration of the liver was performed and cytology results confirmed a cholangiocarcinoma. Generally, the outcome for cholagiocarcinoma is poor and there is limited information regarding the prognosis for patients with cholangiocarcinoma following chemotherapy or surgery.

Keywords: Liver, Tumor, Cat

INTRODUCTION

The prevalence of primary hepatobiliary neoplasia in cats accounts for 1.5-2.3% of all feline neoplasia (Balkman, 2009). Primary hepatobiliary neoplasia is more common than metastatic disease in cats while in dogs liver metastases are more frequent (Pastor and Palnellas, 2013).

Primary hepatobiliary neoplasia can develop from the hepatocytes (hepatocellular adenoma, hepatocellular carcinoma); bile duct epithelium (biliary adenoma, biliary carcinoma); neuroendocrine cells (neuroendocrine carcinoma or carcinoid); or stromal cells (sarcomas). Other neoplastic conditions that often involve the liver include lymphoma, disseminated histiocytic sarcoma, and systemicmastocytosis (Balkman, 2009).

Bile duct neoplasia can be further divided into cholangioadenoma and cholangiocarcinoma. Cholangioadenomas are benign tumours which are common in cats, accounting for 32-52% of all feline hepatobiliary neoplasia. Also known as biliary or cyst adenomas due to their cystic appearance. Cholangioadenomas usually do not cause clinical signs until they reach a large size and compress adjacent organs (Liptak, 2006; Pastor and Palnellas, 2013). Moreover, malignant transformation of cholangioadenoma has been reported in humans and cats (Adler and Wilson, 1995).

Cholangiocarcinoma is the most common malignant hepatobiliary tumour in cats and the second most common in dogs (Liptak, 2006; Pastor and Palnellas, 2013). It can be intrahepatic, extrahepatic, or within the gallbladder. Intrahepatic carcinomas are more common in dogs, while an equal distribution of intrahepatic and extrahepatic carcinomas has been reported in cats. However, bile duct carcinoma of the gallbladder is rare in both species (Lawrence *et al.*, 1994; Cullen and Popp, 2002; Liptak, 2006).

Cholangiocarcinomas have an aggressive biologic behavior. Metastasis is common in dogs with up to 88% metastasising to the regional lymph nodes and lungs and other sites including the heart, spleen, adrenal glands, pancreas, kidneys, and spinal cord (Lawrence *et al.*, 1994; Cullen and Popp, 2002; Liptak, 2006; Pastor and Palnellas, 2013). In cats, diffuse intraperitoneal metastasis occurs in 67-80% of the cases (Lawrence *et al.*, 1994).

Three morphologic forms have been descripted: lobular, multifocal and diffuse. Massive form involving a large mass in one lobe, nodular with discrete nodules in several lobes, or diffuse where the entire liver or part of it is infiltrated with neoplastic cells. In general, only the lobular form should be considered for surgical removal as long as there is no evidence of metastasis. The prognosis for multifocal and diffuse cholangiocarcinoma is poor, and surgery usually is not feasible (Balkman, 2009; Pastor and Palnellas, 2013). Unfortunately, there is no effective chemotherapeutic options for cholangiocarcinoma in cats and dogs.

CASE REPORT

A 7-year-old, spayed female Domestic Shorthair cat was referred to University Veterinary Hospital (UVH), UPM for diagnostic workup of a hepatomegaly as observed on abdominal radiographs (Figure 1 & 2). She was kept with another 50 cats at home, indoor, and fed with commercial dry food. The owner noticed the cat was having distended abdomen 1 week prior to presentation and taken to a private veterinary clinic. Clinically the cat was doing fine. Physical examination findings revealed all vital signs were within the normal range, the cat had a

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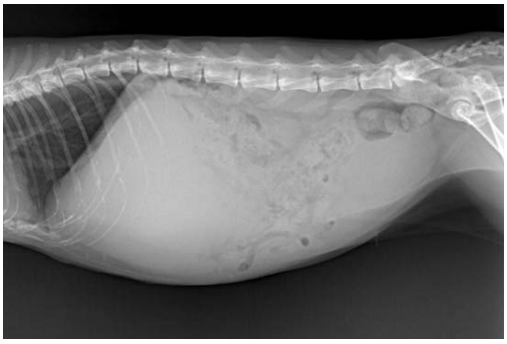

Figure 1. Lateral abdominal radiograph with an enlarged liver

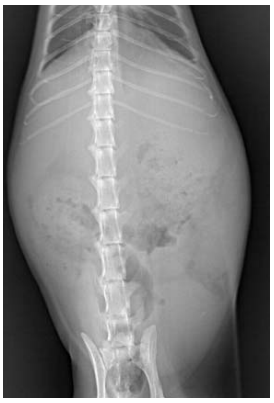

Figure 2. Dorsoventral view of the abdominal radiograph with an enlarged liver

distended abdomen and a hard mass was palpated at the cranial abdomen.

Haematology results showed there was a mildly regenerative anaemia with PCV 0.22 L/L (reference range: 0.24-0.45 L/L) with reticulocytes 1.6/100 RBC (reference range: 0.5-1.5/100 RBC); neutrophilia with left shift (segmented neutrophils 21.13 × 10^9/L, reference range: 2.5-12.5 × 10^9/L; band neutrophils 0.56 × 10^9/L, reference range: <0.3 × 10^9/L) and monocytosis (1.11 × 10^9/L, reference range: 0.2-0.8 × 10^9/L). Serum biochemistry revealed a 10-fold elevation in gamma-glutamyltranspeptidase (GGT) (68 U/L, reference range is <6.0 U/L) indicative of cholestasis or biliary hyperplasia. From the blood result, hepatobiliary disease was evident. Patients with hepatobiliary disease can be anaemic as a result of gastrointestinal bleeding secondary to pressure changes in the liver.

Thoracic radiographs were taken for metastatic check. However, there were no signs of metastasis observed upon thoracic radiography. Abdominal ultrasonography revealed heterechoic liver lobes with irregular margins and presence of nodular and cyst-like structures predominantly affecting the left lobes (Figure 3). A mild ascites was also noted. Therefore, a fine needle aspiration of the liver was performed. Cytology showed a dense aggregate of large epithelial cells with minimal cytoplasm, the fine bluish granules in the cytoplasm of the hepatocytes were consistent with lipofuscin pigment (Figure 4). The cytology result confirmed a cholangiocarcinoma.

The only treatment for cholangiocarcinoma is surgical removable, however in this case more than ¾ of liver was affected therefore lobectomy was not feasible. Chemotherapy for liver neoplasia is questionable. Therefore, only liver supplement (Liv 52 PO BID) was

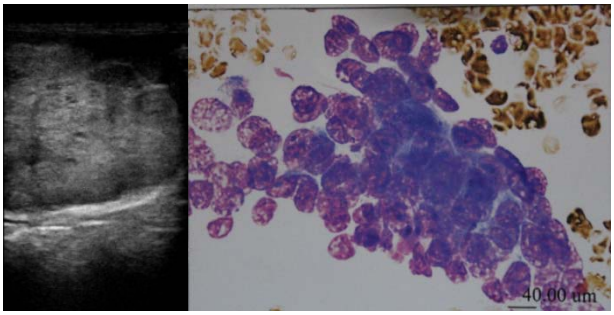

Figure 3. (Left) Abdominal ultrasonography findings were nodular structures on the liver
Figure 4. (Right) Cytology: a cluster of epithelial cells with multiple nucleoli

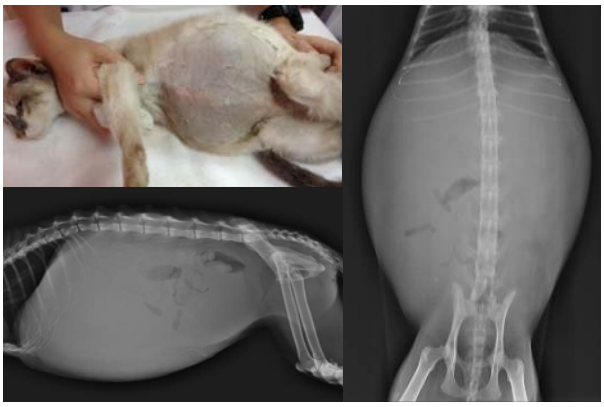

Figure 5. (Top left) Cat presented with distended abdomen with thinning of skin after one month; (Top right and bottom left) Abdominal radiograph after one month, loss of serosal details

given in order to slow down the oxidative damage. The cat deteriorated progressively. She became cachexic, the abdomen distension worsened, she became hyporexic and developed polyuria-polydipsia after one month (Figure 5).

Abdominocentesis was performed in order to reduce the discomfort and 400 mL of hemorrhagic exudate was removed. After one month, abdominal radiography and blood tests were repeated. Abdominal radiography showed general loss of serosal details (Figure 5). Complete blood count showed moderate thrombocytopenia (112 × 10^9/L, reference range: 300-700 × 10^9/L). Thrombocytopaenia can be due to decreased thrombopoeitin production or increased thrombocyte consumption due to gastrointestinal bleeding. Serum biochemistry results showed all the liver enzymes were decreased to lower limit (alanine aminotransferase 17.5 U/L, reference range: 10-90 U/L; alkaline phosphatase 27 U/L, reference range: <80 U/L; gamma-glutamyltranspeptidase 43U/L , reference range : <6 U/L). Decreased liver enzymes values could be the indicative of loss of liver mass. The owner was advised to consider the option of euthanasia due to the deteriorating condition, but the owner chose to spend some quality time with the cat.

DISCUSSION

The liver has significant structural and functional reserve capacity to support ongoing metabolic needs during liver injury. Since the liver has 80% reserve capacity, symptoms occur only in progressive disease whereby the hepatic reserve has been exhausted. Diseases often remain subclinical for long periods of time. As in this case, although most of the liver lobes were affected, the cat was clinically still doing fine and did not show any clinical signs initially. However, when the functional reserve was exhausted, the cat deteriorated very fast.

In humans, the risk factors for cholangiocarcinoma include trematode infestation, cholelithiasis, and sclerosing cholangitis (Boris and Gores, 2008). Trematode infestation such as *Clonorchis sinensis* and *Opistorchis viverrini* associated with the development cholangiocarcinoma are well defined in humans (Sripa *et al.*, 2007). Trematode infestation may also be one of the risk factors for the development of cholangiocarcinoma in cats and dogs. *Platynosum fastosum* infestation has been reported to cause cholangiocarcinomas in cats suggesting an association between the parasitic infection and the carcinogenesis, probably preceded by dilation and thickening of the biliary duct walls, ductal epithelium hyperplasia, and fibrosis (Andrade *et al.*, 2012).

Generally, most hepatobiliary neoplasia shows the same clinical symptoms. Clinical signs and laboratory signs are nonspecific. The most common presenting signs are nonspecific, such as inappetence, weight loss, lethargy, vomiting, polydipsia-polyuria, and ascites (Cullen and Popp, 2002; Liptak, 2006). In this case, the first clinical sign seen was ascites, and progressively the cat showed other symptoms such as inappetance, weight loss and polyuria, polydipsia. Hematologic and serum biochemical abnormalities are usually nonspecific. For the laboratory tests, only GGT was increased in this case, indicative of biliary disease and is not very helpful in making a diagnosis.

Liver lobectomy is recommended for cats and dogs with massive bile duct carcinoma. However, survival time has been poor in cats and dogs treated with liver lobectomy as the majority died within 6 months due to local recurrence and metastatic disease (Lawrence *et al.*, 1994).There is no known effective treatment for cats and dogs with nodular or diffuse bile duct carcinomas as these lesions are not amenable to surgical resection and other treatments are often not successful (Pastor and Palnellas, 2013).

In human medicine, systemic chemotherapy used for cholangiocarcinoma includes single agent gemcitabine; combination of gemcitabine and cisplatin; gemcitabine and oxaliplatin; combination of epirubicin, cisplatin and 5-fluorouracil; oxaliplatin and cisplatin; and combination of sorafenib with lapatinib or bevacizumab (Marsh *et al.*, 2012). However benefits of chemotherapy are still uncertain owing to the lack of truly effective chemotherapy. In veterinary medicine, a gemcitabine-carboplatin combination hasbeen described for cats with carcinoma (Martinez-Ruzafa *et al.*, 2009).However, a gemcitabine-carboplatin combination was showed to be more effective for cats with pancreatic carcinoma. Whereas, this combination appears moderately well tolerated in cats; usage of this combination still limited due to lack of proper dosing and treatment schedules (Martinez-Ruzafa *et al.*, 2009).

Novel treatment such as chemoembolization, microbrachytherapy and antiangiogenic therapy havebeen described in human medicine as treatment options for hepatobiliary neoplasia. Microbrachytherapy is an intraarterialradio embolization using microspheres incorporated with the high energy radionuclideyttrium-90 which is a potential treatment option for patients with unrestectable neoplasia. Once infused, these microspheres traverse the hepatic vascular plexus and selectively implant within the tumour arterioles. Embedded within the arterioles, the impregnated microspheres emit high energy and low penetrating radiation doses selectively to the tumour and causing tumour cell necrosis (Bult *et al.*, 2012). In one pilot study, 3 cats with unresectable liver tumours (hepatocellular carcinoma, cholangiocarcinoma and malignant epithelial liver tumour) were included (Bult *et al.*, 2013).A rather different approach from intraarterial microsphere implantation, this study directly injected radionuclide microsphere into the tumour. All cats improved markedly after treatment and most biochemical and hematologic parameters normalized shortly after treatment. However, these cats were euthanized few months later owing to disease progression. This technique might not be able to prolong the median survival time, but it indicated that holmium 166 acetylacetone microsphere is safe to use and the potential of its' use as a novel intratumoural radioablation device especially for unresctable malignant tumours.

CONCLUSION

Cholangiocarcinoma is a malignant tumour which commonly occurs in old animals. Prognosis for this case was guarded as most of the liver lobes were affected and generally the outcome for cholagiocarcinoma is poor.

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CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest to declare.

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REFERANCES

Adler R. and Wilson D.W. (1995). Biliary cystadenomas of cats. Veterinary Pathology 32:415.

Andrade R.L.F.S., DantasA.F.M., PimentelL.A., Galiza G.J.N., Carvalho F.K.L., Costa V. M.M., Riet-CorreaF. (2012). Platynosomum fastosum-induced cholangiocarcinomas in cats. Veterinary Parasitology 190:277 –280.

Balkman C. (2009). Hepatobiliary Neoplasia in Dogs and Cats. Veterinary Clinical Small Animal Practice. 39:617-625.

Boris R.A., and Gores G.J. (2008) Cholangiocarcinoma. Clinical Liver Disease. 12:131-150

Bult W., Leeuw H.D., Steinebach O.M., Martijn JB.et al. (2012) Radioactive Holmium Acetylacetonate Microspheres for Interstitial Microbrachytherapy: An In Vitro and In Vivo Stability Study. Pharmaceutical Research. 29:827–836

Bult W., Vente M.A., Vandermeulen E., Gielen I., Seevinck P.R., Saunders J. et al (2013). Microbrachytherapy using holmium-166 acetylacetonate microspheres: a pilot study in a spontaneous cancer animal model. Brachytherapy. 12:171-177.

Cullen J.M., Popp J.A. (2002). Tumours of the liver and gall bladder. In Meuten D.J. (4thed): Tumours in domestic animals. Ames. Iowa State Press.

Lawrence H.J., Erb H.N., Harvey H.J. (1994). Nonlymphomatous hepatobiliary masses in cats: 41 cases (1972–1991). Veterinary Surgery 23:365.

Liptak J.M. (2006). Section F Hepatobiliary Tumours. In: Withrow S. and Vail D. (4th Ed). Withrow and MacEwen's Small Animal Clinical Oncology. Saunders. pp483-490

Marsh R. et al (2012). Comprehensive review of the diagnosis and treatment of biliary tract cancer 2012. Part II: Multidisciplinary Management. Journal of Surgical oncology.106:339–345

Martinez-RuzafaI., Dominguez P.A., Dervisis N.G., Sarbu L., Newman R.G., Cadile C.D., and Kitchell B.E. (2009). Tolerability of Gemcitabine and Carboplatin Doublet Therapy in Cats with Carcinomas. Journal of Veterinary Internal Medicine. 23:570–577

Pastor J. and Palnellas M. (2013). Neoplastic disorders. In Wasahbau R.J. and Day M.J.(2nd Ed).: Canine & feline gastroentology. Elsevier. Pp914-922

Sripa B., Kaewkes S., Sithithaworn P., Mairiang E., Laha T., Smout M. et al. (2007). Liver flukes induces cholangiocarcinoma. Public Library of Science Medicine. 4:1148–1155

Weisse C. (2009). Hepatic Chemoembolization: A Novel Regional Therapy. Veterinary Clinical Small Animal Practice. 39:627-630.