Cholangiocarcinoma of intrahepatic bile ducts with disseminated metastases in a Siamese cat: a case report

O. Aslan[1], L. Cakir[1], I.K. Bekdik[1], Z. Dogan[1], A.S. Tunc[2]

[1]Faculty of Veterinary Medicine, Erciyes University, Kayseri,Turkey
[2]Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

ABSTRACT: This case report concerns a four-year-old female Siamese cat which presented with inappetence, vomiting and weight loss. During routine clinical examinations of the patient, numerous neoplastic masses were detected in the liver, lungs and abdomen. Upon a request from the owner, the cat was euthanised. At necropsy, the primary tumour was detected in the liver. The tumour was greyish-white, firm, and multi-nodular. There were metastases in the portal lymph nodes, diaphragm, omentum, colon, caecum and lungs. Histologically, the tumour was characterised by a tubular pattern with periodic acid-Schiff- positive secretory material in glandular and canal structures. The neoplastic cells were positive to broad-spectrum cytokeratin. Histochemical and immunohistochemical stains were consistent with an intrahepatic bile duct carcinoma. This is the first case to report the metastasis of a cholangiocellular carcinoma to the colon in cats.

Keywords: cat; cholangiocellular carcinoma; colon; Siamese

Cholangiocellular carcinoma (CC) is a term used for malign liver tumours originating from intrahepatic and extrahepatic bile duct epithelium (Jacobs and Snyder 2007). Post and Patnaik (1992) reported that 53% of primary liver tumours in cats represent intrahepatic CC; their study of 21 cats with non-haematopoietic liver tumours found that six cats (28.5%) had CC. The tumour is commonly found in animals older than 10 years and there are no breed (Post and Patnaik 1992) or sex predispositions (Adler and Wilson 1995; Cullen and Poop 2002) associated with it. However, Post and Patnaik (1992) reported a predisposition to the tumour in male cats. On the other hand, in humans and dogs, the tumour is observed more commonly in females. The pathogenesis of the tumour in females was found to be related to bile duct hyperplasia reflecting the involvement of hormones (Patnaik et al. 1980; Kurashina et al. 1988).

The aetiology of bile duct tumours remains poorly understood. However, it has been associated with *Clonorchis sinensis*, a trematode frequently found in natural and experimental cases in cats and humans in southeast Asia (Hou 1964; Thamm 2001; Choi et al. 2004). In addition, prolonged exposure to *o*-aminoazotoluene and aramite, a sulphur-containing compound used for insecticide purposes, may cause CC (Cullen and Poop 2002). Other risk factors for bile duct tumours in humans are bile duct stones and sclerosing cholangitis (Hammer and Sikkema 1995; Thamm 2001). Hepatitis B virus which causes chronic hepatitis in humans and laboratory animals; Woodchuck hepatitis virus; and mycotoxins such as anatoxins have also been shown to cause hepatobiliary tumours (Miller et al. 1985; Munro and Youngson 1996). The molecular mechanisms underlying cancer initiation and progression are ambiguous (Okuda et al. 2002; Olnes and Erlich 2004; Sirica 2005). However, given that the tumour glands morphologically resemble cholangioles, a suggestion can be made that CC is formed from the Hering ducts (Theise et al. 1999).

The clinical symptoms in cats with CC vary and are not differential. There may not be liver-specific symptoms either. Early diagnosis of cholangiomas is not possible due to the absence of specific clinical symptoms in most cases (Cullen and Poop 2002). Cats with CC show some general symptoms such as anorexia, lethargy, vomiting, and weight loss. Ascites are rarely observed; however, serum liver enzymes, bile acids and bilirubin increase (Hammer

and Sikkema 1995; Thamm 2001; Moore and Ogilvie 2001; Liptak et al. 2004). In ultrasonic examination of cases of CC, mottling, losses of surface contour and hyperechogenicity in liver have been reported (Moore and Ogilvie 2001).

The general necropsy findings in CC are usually defined by one or more firm and white masses that are slightly deflated in the middle, papillary and tending to be well delineated. These are round- or cauliflower-shaped masses located on the liver surface. The section surface of the neoplastic tissue is seen as white and may include necrotic and haemorrhagic areas (Ciftci et al. 1998). In this case, the middle of the tumour is generally appears as necrotic, haemorrhagic and cystic. The enlargement of the liver is also a serious symptom associated with CC. The tumour may not always be bordered distinctively due to its invasive characteristics (Munro and Youngson 1996). CC tumours consist of cubic and cylindrical cells with homogenous and sometimes granular eosinophilic cytoplasm, resembling bile duct epitheliums. The neoplastic cells in well-differentiated tumours are in ordered and small acinuses. They do not invade healthy tissue. Although the structure of this type of tumour resembles an adenoma, it harbours high malignant potential (Cullen and Poop 2002). The majority of invasive tumours may metastasise to the peritoneum, mesentery and intestine wall via a transperitoneal route; to lymph nodes through lymphatics; and to lungs, kidneys, spleen, thyroid, upper kidney gland and bone marrow through a haematogenic way (Cullen and Poop 2002). Malign bile duct tumours are rarely observed and their prognosis is generally poor (Post and Patnaik 1992; Lawrence et al. 1994; Liptak et al. 2004). Malign-type bile duct tumours in cats are generally localised to the liver in which their multi-nodular structure is an impediment to surgical removal (Lawrence et al. 1994; Shiga et al. 2001; Lepri et al. 2013).

Histological distinction among cholangiocellular carcinoma, hepatocellular carcinoma and metastatic tumours (renal cell carcinoma, poorly differentiated adenocarcinoma, malignant melanoma) is quite difficult (Kakar et al. 2003). Immunohistochemical staining methods are widely used for the distinction of these types of tumours in humans (Balaton et al. 1988; Kakar et al. 2003). Monoclonal antibodies including hepatocyte paraffin 1 (Hep Par-1), cytokeratin 7(CK7), cytokeratin 19(CK19), alpha fetoprotein (AFP) are used effectively to differentiate cholangiocellular carcinoma and hepatocellular carcinoma (Balaton et al. 1988; Kakar et al. 2003; Martin De Las Mulas et al. 1995).

Hep par 1 is a recently described monoclonal antibody that is highly sensitive and specific for hepatocellular differentiation. Cholangiocarcinomas and carcinomas from most other sites are negative for Hep Par 1 (Kakar et al. 2003). CK7 and CK19 are of prognostic value in hepatocellular carcinomas as well as in distinguishing cholangiocarcinomas from hepatocellular carcinomas. Therefore, CK7 and CK19 are useful markers of bile ducts (Balaton et al. 1988).

AFP is a very specific but not very sensitive marker of hepatocellular differentiation (Martin De Las Mulas et al. 1995).

Case description

This study concerns a four-year-old female Siamese cat presenting with inappetence, vomiting and weight loss, admitted to the Faculty of Veterinary Medicine Clinics at Erciyes University. Clinical, biochemical and radiological examinations of the cat were performed.

Serum biochemical analysis revealed the levels of glucose, BUN, creatinine, GGT, AST, ALT, ALP, total protein, total bilirubin, direct bilirubin, amylase, lipase and Ca to be 69 mg/dl, 53 mg/dl, 1.2 mg/dl, < 4 IU/l, 44 IU/l, <6 IU/l, 13 IU/l, 5.7 g/dl, 0.1 mg/dl, < 0.1 mg/dl, 945 IU/l, 87 IU/l, and 8.6 mg/dl, respectively.

Ultrasonographic examination of the abdomen revealed free abdominal fluid, hepatomegaly, and several hypoechoic areas in which anechoic, limited structures 0.5–4 cm diameter in size were found in

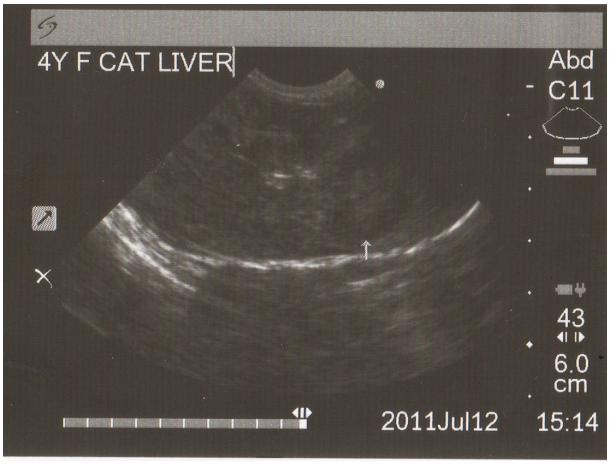

Figure 1. Isolated hypoechoic area (arrow) where anechoic structures were found in the liver

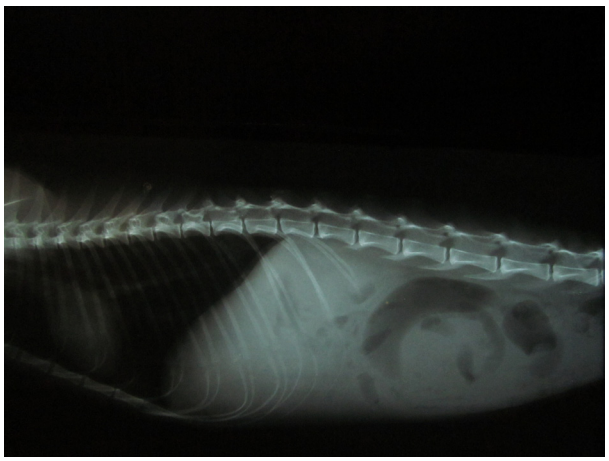

Figure 2. Radiographic image

the liver parenchyma (Figure 1) and mesentery area. Radiological examination revealed a detail-loss in the abdomen. Irregularity of liver outline and hepatomegaly were detected upon the application of pressure to the stomach. A part of the small intestines was expanded with gas. Stenosis was observed in the expanded section at one point, indicating obstruction. Also, radiolucent areas were present in the lungs (Figure 2). Upon the request of the owner, the cat was euthanised and a necropsy was performed.

The liver and metastatic tissue specimens were fixed in formalin solution and embedded in paraffin, forming 4 µm-thick sections. The tissue sections were stained with haematoxylin and eosin (HE) and periodic acid-Schiff (PAS) for histological examination. The immunohistochemical staining was performed using the standard avidin-biotin peroxidase complex method (ABC, Dako, Carpinteria, USA). Two hepatocyte markers (Hep Par 1 and α-fetoprotein), two cholangiocyte markers (CK 7,CK 19) and CK (AE1/AE3) were used. Briefly, the slides were incubated in the following primary antibodies: CK (AE1/AE3; Dako, dilution

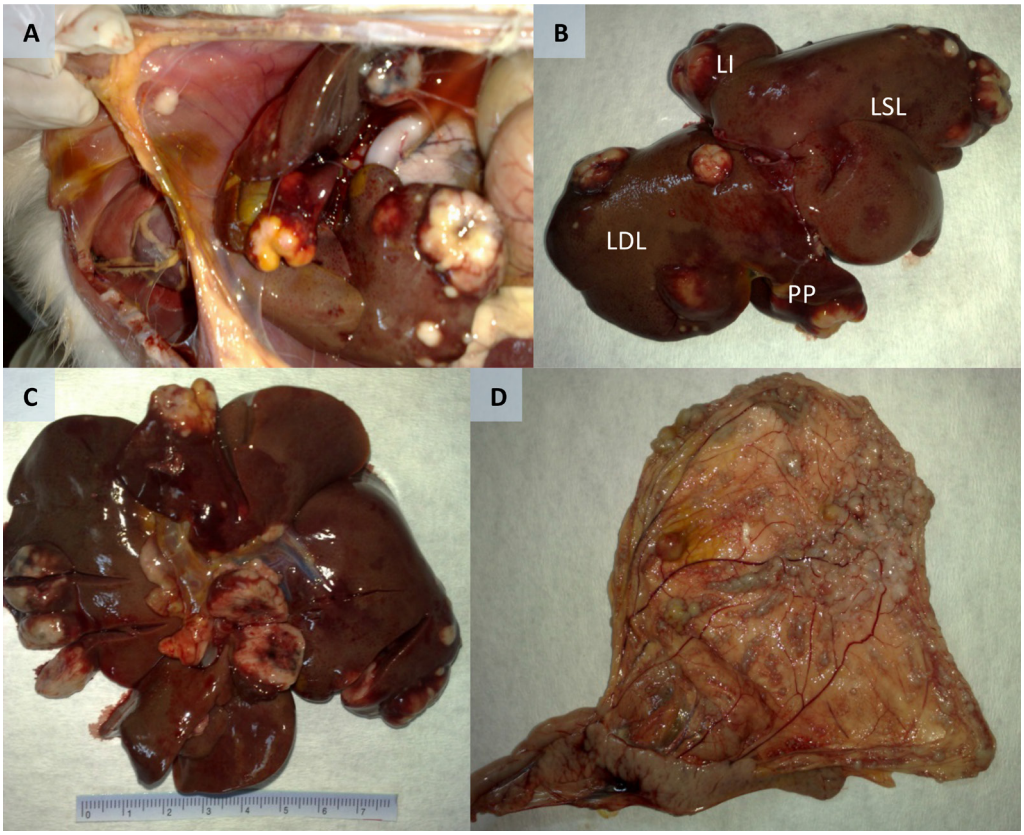

Figure 3. (**A**) Cholangiocellular carcinoma. Nodular structures in the diaphragmatic surface of the liver. The neoplastic tissue in the sternal part of the diaphragm (arrow). (**B**) The macroscopic image of lobes with tumours on the diaphragmatic surface of the liver. Note the presence of neoplastic tissue of different sizes on the dorsal edge of the *lobus dexter lateralis* (LDL) and close to the dorsal edge; on the ventral edge of the *lobus dexter medialis* in the prosesus papillaris of the *lobus intermedius* (LI) and *lobus caudatus* and in the *lobus sinister lateralis* (LSL). (**C**) The visceral surface of the liver with tumour. Multi-nodular neoplastic tissue of different sizes in all lobes and the macroscopic image of centrally haemorrhagic and necrotic section surfaces of tumours. (**D**) Metastatic foci in the omentum

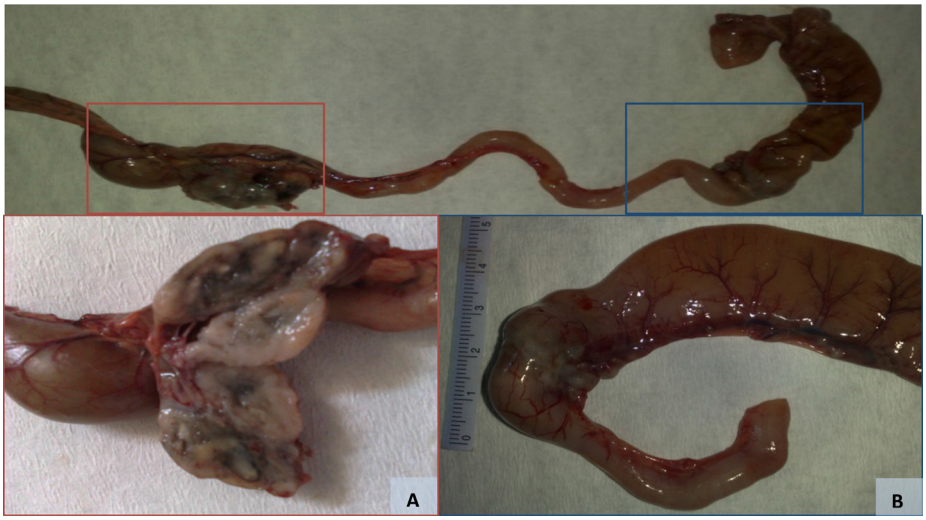

Figure 4. Neoplastic tissue in the caecum (area in red) and colon (area in blue). (**A**) The section surface of the neoplastic tissue in the caecum and ileocecal lymph nodule. (**B**) The neoplastic tissue filling the colon lumen

1 : 500, USA), CK19 and anti-alpha fetoprotein (anti-AFP) (Neomarkers, Thermo Fisher Scientific, dilution 1 : 200,), CK7 (Biogenex, dilution 1 : 200), Hep Par 1 (Neomarkers, Thermo Fisher Scientific, dilution 1 : 20). Negative control sections were processed following the same procedure as described above; however, primary antibodies were excluded.

The abdominal cavity contained 300 ml liquid with blood. Greyish-white, firm and multifocal neoplastic structures of sizes varying between 0.5

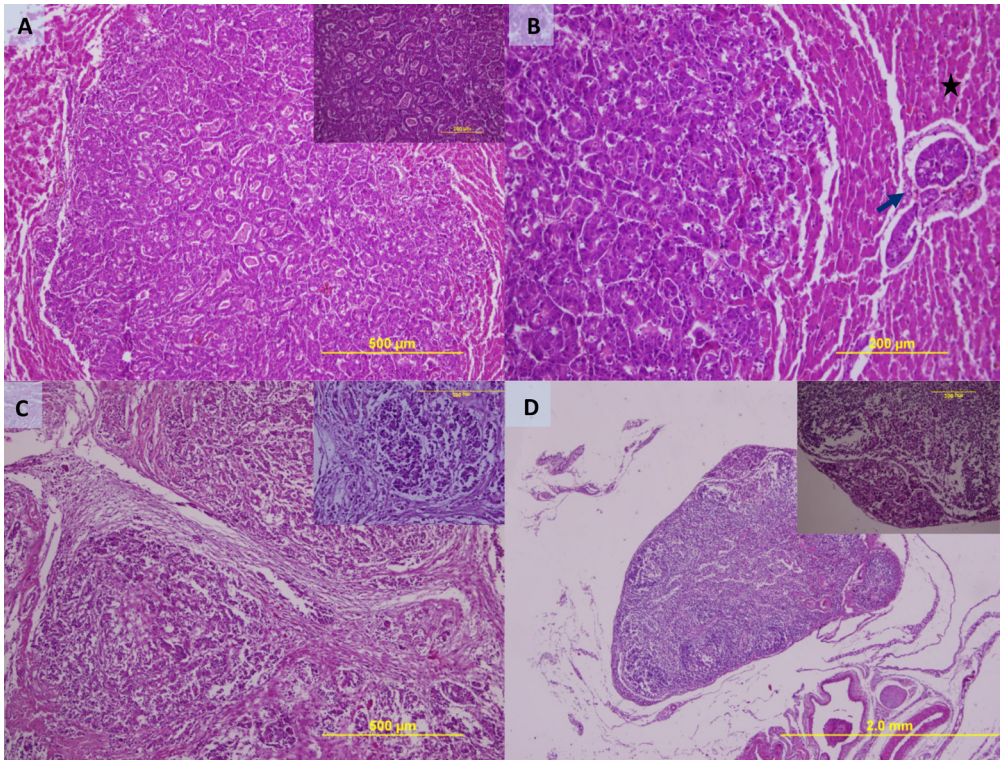

Figure 5. (**A**) Canal- or gland-shaped arrangements of tumour cells in the liver; H×E. Inset shows higher magnification of glandular and canal structures the lumens of which are filled with mucus fluid. (**B**) Malign tumour emboli in the portal vein (arrow). Note vascular invasion which is a risk factor for intrahepatic metastasis. Liver tissue outside the tumour area (star). (**C**) Poor-differential tumour cells omentum; H×E. Inset shows higher magnification. (**D**) Metastatic lymph nodes; the tumour cells invaded through the subcapsule sinus of the lymph node. Inset shows higher magnification

and 4 cm in diameter were found on both the outside and the cross section surface of the liver. It was noted that the middle of neoplastic tissues in the liver was slightly deflated and papillary. There were also many nodules of up to 2 cm in diameter in the sternal part of the diaphragm, in the portal and mesentery lymph nodes, and on the parietal peritoneum and omentum (Figure 3). Nodules of 2.5–3 cm and 2–2.5 cm in diameter were observed in the distal 1/3 of the colon, and mesocolon and its mucosa, respectively, with the latter surrounding the caecum wall throughout (Figure 4). In addition, two grey-white nodules of 0.5–1 cm in diameter were found in the cross section surface of the lung.

The tumour parenchyma was formed by cubic and columnar cells with vesicular, chromatin-poor nuclei. Whilst the nucleus in columnar cells was situated in the base of the cell and was oval-shaped, in cubic cells, it was found in the centre of the cell and was rounded. The cytoplasm was slightly granular and pale eosinophilic. These cells formed glandular or canal structures, usually by aligning side-by-side (Figure 5A–C). The lumens of some of these structures were found to be empty; however, most of them were filled with pink-red mucus secretion in sections stained with PAS and mucicarmine. The neoplastic tissues were characterised by a lobular structure, connective tissue trabeculles of different thickness and a vast number of hyperaemic blood vessels in the stroma. Emboli of tumour cells were found in lymph ducts and blood vessels in the liver. The metastatic tumours in the lungs, colon (Figure 5D), caecum, diaphragm and omentum were of similar structure to those in the liver. The neoplastic tissue was found to have replaced the lymphoid tissue in the portal and mesentery lymph nodes which also had similar characteristics to those in the liver. Sections obtained from lymph nodes showed that the mass of neoplastic tissue formed cell cordons that began from the vascular walls and ran through thin connective tissue septums. Limited numbers of glandular and canal-type structures were noted (Figure 6). Immunohistochemistry revealed a focally intense CK (AE1/AE3) (Figure 7), CK 19 and CK 7 immunoreactivity both in the primary and metastatic nodules. On the other hand, the slides were negative for AFP and Hep Par 1 (Figure 8).

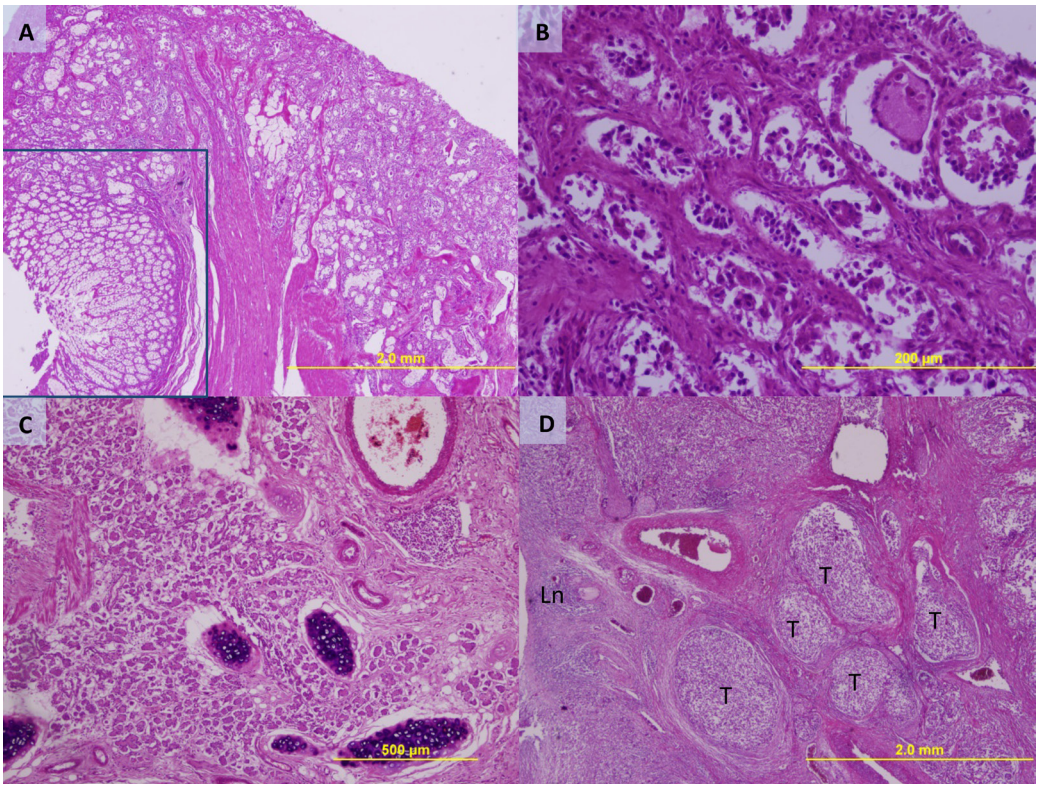

Figure 6. Metastatic intrahepatic CC. (**A**) Irregular invasive tumour glands and cords extending beyond the muscularis propia of the wall into the subserosal tissue of the colon (area in blue). (**B**) Higher magnification of Figure (A). (**C**) The metastatic tumour formed glandular and canal structures, lung. (**D**) Loss of lymphoid tissue due to a common metastasis in the mesenteric lymph nodes (Ln); neoplastic tissue (T); H×E

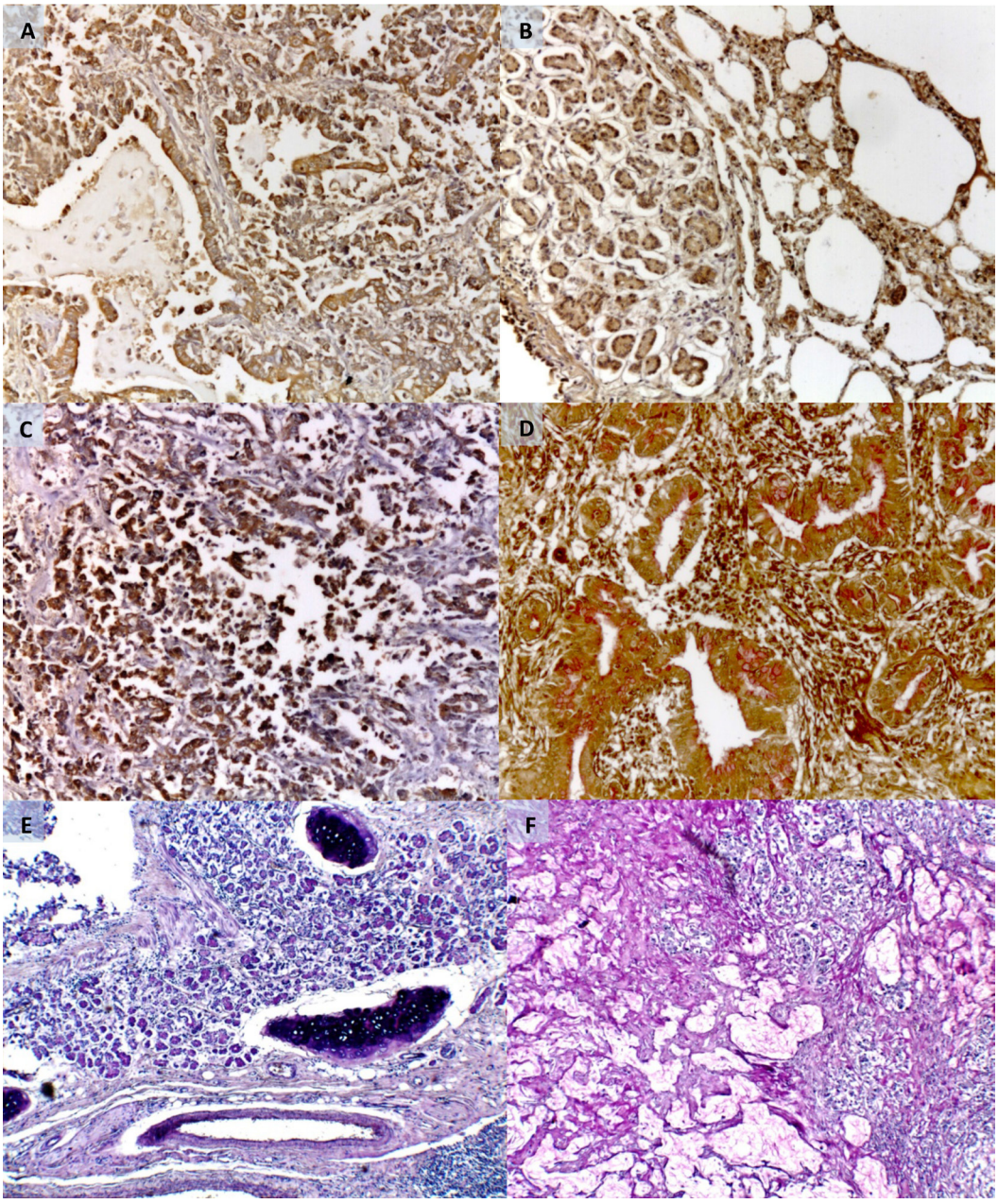

Figure 7. Cytokeratin (AE1/AE3) staining in the cholangiocellular area (A) to (C). Avidin-biotin-peroxidase method, Mayer's haematoxylin counterstain. (**A**) Caecum, 400×; (**B**) lung, 200×; (**C**) liver, 200×. (**D**) The cytoplasm of the cells lining this neoplastic gland in a cholangiocarcinoma are pink with the mucicarmine stain, 400×. (E) to (F) PAS-positive cytoplasm/lumen in metastatic cholangiocarcinoma. (**E**) Lung, 200×; (**F**) caecum, 200×

DISCUSSION AND CONCLUSIONS

Cholangiocellular carcinoma (CC) denotes malign liver tumours that arise from intrahepatic and extrahepatic bile duct epithelium (Jacobs and Snyder 2007). The tumour has usually been found in animals older than 10 years. There have been no studies reporting breed (Post and Patnaik 1992) or gender predispositions (Cullen and Poop 2002) associated with this tumour except that Post and Patnaik (1992) stated that the tumour was found more commonly in male cats. In our study, the Siamese cat in which we identified the CC was a female as has been reported in humans and dogs (Patnaik et al. 1980; Kurashina et al. 1998). It is rather rare that a metastatic CC is found in cats as young as four years old as in our case.

CC may be caused by the trematode *Clonorchis sinensis*; exposure to *o*-aminoazotoluene and sulphite compounds used as insecticides for a long

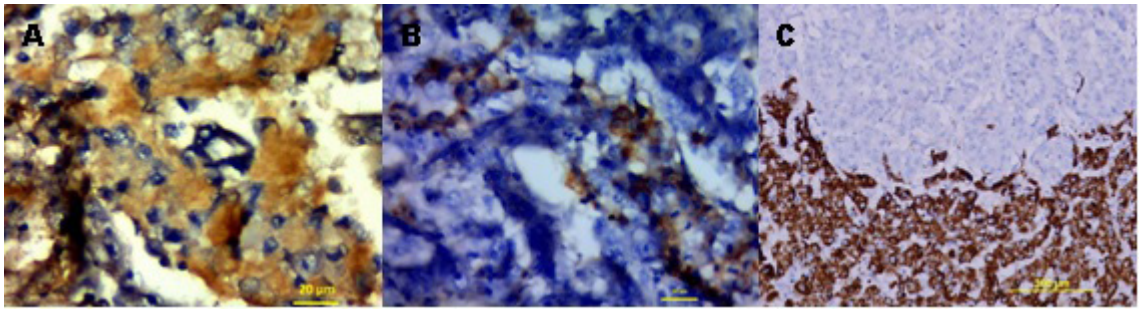

Figure 8. (**A**) Cytokeratin 19 and (**B**) cytokeratin 7 staining in the cholangiocellular area; 20×. (**C**) The interphase between the infiltrating margin of the cholangiocellular carcinoma and non-neoplastic liver parenchyma. There is strong staining of the latter with Hep Par 1. In contrast, the neoplastic tissue is virtually unstained. Avidin-biotin-peroxidase method, Mayer's haematoxylin counterstain

time in cats and humans; bile stones; and sclerosing cholangitis in humans (Hou 1964; Hammer and Sikkema 1995; Thamm 2001; Cullen and Poop 2002; Choi et al. 2004). *Clonorchis sinensis* was not detected in this study. We were also informed that the cat was not at all exposed to *o*-aminoazotoluene and aramite.

The clinical findings of cats with CC vary greatly and the general symptoms reported in most cases include anorexia, lethargy, vomiting, weight loss, and on rare occasions ascites (Post and Patnaik 1992; Lawrence et al. 1994; Hammer and Sikkema 1995; Moore and Ogilvie 2001; Thamm 2001), which are in agreement with the clinical symptoms found in this study, such as anorexia, vomiting, apathy, mild dehydration, cachexia, pale mucosa and ascites. Cats with CC exhibit increased levels of serum liver enzymes, bile acids and bilirubin (Lawrence et al. 1994; Hammer and Sikkema 1995; Thamm 2001; Moore and Ogilvie 2001). Post and Patnaik (1992) reported a tendency for serum ALT and AST levels to increase in 21 cats with non-haematopoietic hepatic neoplasms. They also found that clinical findings and serum enzyme activities were not differential for hepatic neoplasms. In addition, Uygun and Polat (2009) indicated that some liver function test results may give values within reference levels in cases of inactive cirrhosis, hepatocellular carcinoma, and portal hypertension, causing complications that are life threatening. In contrast to other studies, the normal or reduced levels of all liver enzymes (except for ALT) and bilirubin in our study can be attributed to the reduced functional parenchymal tissue and limited ongoing damage due to a change in the intrahepatic structure.

The ultrasonographic examination in the present case revealed abdominal fluid, hepatomegaly, and many limited hypoechoic areas encompassing anechoic structures in the liver parenchyma. Similar to these findings, Joshita et al. (2009) also defined the ultrasonographic findings of CC as hypoechoic lesions that are non-homogenous and not very well differentiated. Jacobs and Snyder (2007) also reported abdominal free fluid, non-uniform liver border, common hyperechoic areas and mottling in the liver in the ultrasonographic examination of a cat with CC. In addition, Catalo et al. (2005) found hypoechoic, necrotic areas with thin walls and definite hypoechogenity in the portal and sinusoidal phase images of the CC. Given the ultrasonographic images examined in this study, it can be suggested that the CC was in the portal and sinusoidal phase.

The necropsy findings of CC are generally characterised by white, rounded or cauliflower-shaped masses on the liver surface that are multi-nodular and slightly deflated in the middle and papillary. Sections of neoplastic tissues may also be white and in some cases include necrotic or haemorrhagic locations (Ciftci et al. 1998). In the present case, the neoplastic tissues were also white, rounded, slightly deflated in the middle and papillary in the liver.

To date, there have been a large number of studies reporting the metastasis of CC into the peritoneum, lungs, lymph nodes, diaphragm, spleen, kidneys, heart, adrenals, and the bone marrow (Fucich et al. 1994; Cullen and Poop 2002; Mischke et al. 2003; Ilhan et al. 2008; Lepri et al. 2013). In agreement with earlier results, in the current study it was found that the CC had metastasised into the lungs, portal and mesenteric lymph nodes, peritoneum, colon and the caecum. Previous studies have not reported the metastasis of CC into the colon in domestic and wild animals (Lepri et al. 2013). In

humans, however, CC may metastasise, although rarely, into the colon (Wakahara et al. 2005). We also observed, unlike other studies, metastasis of the CC into the caecum and ileocecal area. The macroscopic and microscopic examinations of the gallbladder in the present case revealed a homogenous distribution of the nodules across the hepatic lobes, which were considered to originate from the intrahepatic bile duct. The histological findings of the intrahepatic CC in this study align well with those reported in the literature in domestic animals (Shiga et al. 2001; Cullen and Poop 2002; Mischke et al. 2003; Ilhan et al. 2008; Lepri et al. 2013).

The CC in this study was diagnosed based on a comparison of the histological changes, analysis of histomorphology and histochemistry and positive staining in immunohistochemistry (IHC). While the histomorphology was employed to probe the presence of a tubular and acinar pattern, histochemistry was used to detect the presence of PAS-positive amorphous material in the lumen of neoplastic acinar and tubular structures. Both the primary and the metastatic tumours showed focally intense broad-spectrum cytokeratin (CK) immunoreactivity in the IHC. The AE1/AE3 marker has been reported to be reliable for marking CC cells in hepatocellular carcinoma (Shiga et al. 2001; Ilhan et al. 2008). No other masses were found in the necropsy that could be confused with secondary tumours.

In this study, it was found that CK7, and CK19 were expressed diffusely in neoplastic cells while AFP and Hep Par 1 was not expressed in biliary ducts and ductules. The combined analysis of CK7, CK19 and Hep Par 1 was useful in the differential diagnosis of HCC (hepatocellular carcinoma) from CHC. In the present case, AFP and Hep PAR 1 were useful in confirming hepatocellular and biliary epithelial differentiation.

In conclusion, as the clinical signs of CC are similar to other digestive system diseases, this study was designed, to point out the possibility of this disease to clinicians, in cats aged about four years suffering from similar clinical signs. Furthermore, to our knowledge, the present case report is the first to describe CC metastasis into the colon in cats.

REFERENCES

Adler R, Wilson DW (1995): Biliary cystadenomas in cats. Veterinary Pathology 32, 415–418.

Balaton AJ, Nehama-Sibony M, Gotheil C, Callard P, Baviera EE (1988): Distinction between hepatocellular carcinoma, cholangiocarcinoma, and metastatic carcinoma based on immunohistochemical staining for carcinoembryonic antigen and for cytokeratin 19 on paraffin sections. Journal of Pathology 156, 305–310.

Catalano O, Nunziata A, Lobianco R, Sian A (2005): Real-time harmonic contrast material-specific us of focal liver lesions. Radiographics 25, 333–349.

Choi BI, Han JK, Hong ST, Lee KH (2004): Clonorchiasis and cholangiocarcinoma: etiologic relationship and imaging diagnosis. Clinical Microbiology Reviews 17, 540–542.

Ciftci MK, Ortatatli M, Avki S (1998): Cholangiocellular carcinoma in a cat (in Turkish). Veteriner Bilimleri Dergisi 14, 91–96.

Cullen JM, Poop JA (2002): Tumours of the liver and gallbladder. In: Meuten DJ (ed.): Tumours in Domestic Animals. 4th ed. Iowa State Pres, Iowa, USA. 495–499.

Fucich LF, Cheles MK, Thung SN, Gerber MA, Marrogi AJ (1994): Primary metastatic hepatic carcinoma. An immunohistochemical study of 34 cases. Archives of Pathology and Laboratory Medicine 118, 927–930.

Hammer AS, Sikkema DA (1995): Hepatic neoplasia in the dog and cat. Veterinary Clinics of North America: Small Animal Practice 25, 419–435.

Hou PC (1964): Primary carcinoma of the bile duct of the liver of the cat (Felis catus) infested with Chonorchis sinesis. Journal of Pathology and Bacteriology 87, 239–244.

Ilhan F, Yener Z, Vural SA, Haligur M (2008): Mucinous cholangiocarcinoma with metastases in a Turkish Van cat – a case report. Bulletin of the Veterinary Institute in Pulawy 52, 131–134.

Jacobs TM, Snyder PW (2007): Mucinous cholangiocarcinoma in a cat. Journal of the American Animal Hospital Association 43, 168–172.

Joshita S, Ichijo T, Suzuki F, Yokoyama T, Sugiyama Y, Fukushima M, Kamijo A, Komatsu M, Umemura T, Yoshizawa K, Miyagawa S, Tanaka E (2009): A case of well differentiated cholangiolocellular carcinoma visualized with contrast-enhanced ultrasonography using Sonazoid. Hepatology Research 39, 207–212.

Kakar S, Muir T, Murphy LM, Lloyd RV, Burgart LJ (2003): Immunoreactivity of Hep Par 1 in hepatic and extrahepatic tumors and its correlation with albumin in situ hybridization in hepatocellular carcinoma. American Journal of Clinical Pathology 119, 361–366.

Kurashina M, Kozuka S, Nakasima N, Hirabayasi N, Ito M (1988): Relationship of intrahepatic bile duct hyperplasia to cholangiocellular carcinoma. Cancer 61, 2469–2474.

Lawrence HJ, Erb HN, Harvey HJ (1994): Non-lymphomatous hepatobiliary masses in cats: 41 cases (1972–1991). Veterinary Surgery 23, 365–368.

Lepri E, Sforna M, Brachelente C, Vitellozzi G (2013): Cholangiocarcinoma of intrahepatic bile ducts with disseminated metastases in an African lion (Panthera leo). Journal of Zoo and Wildlife Medicine 44, 509–512.

Liptak JM, Dernell WS, Withrow AS (2004): Liver tumors in cats and dogs. Compendium on Continuing Education for the Practising Veterinarian 26, 50–56.

Martín De Las Mulas J, Gomez-Villamandos JC, Perez J, Mozos E, Estrada M, Mendez A (1995): Immunohistochemical evaluation of canine primary liver carcinomas: distribution of alpha-fetoprotein, carcinoembryonic antigen, keratins and vimentin. Research in Veterinary Science 59, 124–127.

Miller RE, Boever WJ, Thomburg LP, Curtis Velasco M (1985): Hepatic neoplasia In two polar bears. Journal of the American Veterinary Medical Association 187, 1256–1258.

Mischke R, Hoinghaus R, Lutkefels E, Buhl K, Gerhardt A, Hewicker-Trautwein M (2003): Immunocytological confirmation of bone marrow metastases in a dog with cholangiocarcinoma. Journal of Small Animal Practice 44, 411–414.

Moore AS, Ogilvie GK (2001): Splenic, hepatic and pancreatic tumours. In: Moore AS, Ogilvie GK (eds): Feline Oncology. Trenton: Veterinary Learning Systems. WB Saunders, Philadelphia. 295–310.

Munro R, Youngson RW (1996): Hepatocellular tumours in roe deer in Britain. Veterinary Record 138, 542–546.

Okuda K, Nakanuma Y, Miyazaki M (2002): Cholangiocarcinoma: recent progress. Part 2: Molecular pathology and treatment. Journal of Gastroenterology and Hepatology 17, 1056–1063.

Olnes MJ, Erlich R (2004): A review and update on cholangiocarcinoma. Oncology 66, 167–179.

Patnaik AK, Hurvitz AI, Lieberman H (1980): Canine hepatic neoplasms: A clinicopathologic Study. Veterinary Pathology 17, 553–564.

Post G, Patnaik AK (1992): Nonhaematopoietic hepatic neoplasm in cats: 21 cases (1983–1988). Journal of American Veterinary Medical Association 201, 1080–1082.

Shiga A, Shirota K, Enomoto M (2001): Combined hepatocellular and cholangiocellular carcinoma in a dog. Journal of Veterinary Medical Science 63, 483–486.

Sirica AE (2005): Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. Hepatology 41, 5–15.

Thamm DH (2001): 4.21.F Hepatobiliary tumours. In: Withrow SJ, MacEwen EG (eds.): Small Animal Clinical Oncology. 3rd ed. WB Saunders, Philadelphia. 327–334.

Theise ND, Saxena R, Portmann BC, Thung SN, Yee H, Chiriboga L, Kumar A, Crawford JM (1999): The canals of hering and hepatic stem cells in humans. Hepatology 30, 1425–1433.

Uygun A, Polat Z (2009): Other than viral hepatitis, diseases causing increase in serum transaminase levels (in Turkish). Guncel Gastroenteroloji 13, 211–224.

Wakahara T, Tsukamoto T, Kitamura S, Watanabe A, Tsujimura T, Nakamura Y, Toyokawa A, Onishi N, Hamabe Y, Mukai H, Teramura K (2005): Metastatic colon cancer from intrahepatic cholangiocarcinoma. Journal of Hepato-biliary-pancreatic Surgery 12, 415–418.

Received: 2014–02–20
Accepted after corrections: 2014–08–25

Corresponding Author:

Oznur Aslan, Erciyes University, Faculty of Veterinary Medicine, Department of Internal Medicine, 38039 Kayseri, Turkey
E-mail: oznuratalay@gmail.com