

A cystadenoma of the biliary ducts in a dog: anatomo-histopathological features and pathogenetic considerations: a case report

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ABSTRACT: A rare case of a liver biliary duct cystadenoma in a dog is reported. Tissue changes are described with an emphasis on immunohistochemical patterns that aid in the identification of the tumour and differentiation from similar macroscopical features that arise due to congenital abnormalities. Finally, we provide hints on comparative pathology.

Keywords: biliary ducts cystadenoma; immunohistochemistry; liver neoplasm; pathology; dog

Primitive liver tumours show an incidence of 0.6 to 2.6% in dogs, whilst secondary tumours have an incidence of 30–37%. Among benign epithelial tumours, biliary cystadenomas represent a rare form. They are benign epithelial proliferative tumours, usually with cystic or polypoid features (Short et al. 1971), and have been reported in the literature in different animal species (Moulton 1990). In human medicine, most of these tumours originate from the epithelium of intra-hepatic biliary ducts, although, at a rate of 10–20%, they arise from extra-hepatic ducts, such as the common hepatic duct, choledocum and gallbladder (Kim 2006).

In the literature, this neoplasm is frequently described in cats (Adler and Wilson 1995; Trout et al. 1995; Nyland et al. 1999; Kristick et al. 2010), whereas it has on rare occasion been reported in pigs (Graw and Berg 1977), sheep (Watt 1970) and dogs (Trigo et al. 1982; Akkoc et al. 2009; Moon et al. 2011); moreover, in humans it is a rare tumour with a higher incidence in women older than 40 years (Ishak et al. 1977).

Biliary cystadenomas are often characterised by silent and/or non-specific symptoms and have been described as accidental findings during post-mortem histopathological examinations. As compared to humans, in veterinary pathology, there is no predilection for sex or species. Histologically,

human cystadenomas are characterised by high columnar cells and a dense cellular stroma, which permits differentiation from the same tumour in cats lacking such characteristics. The aetiology of this tumour is unknown.

In this paper, we describe a cystadenoma in a dog, found during routine necropsy, and its anatomo-histo-pathological changes, using diagnostic immunohistochemical tools. Moreover, we compare the results to the same neoplasm in humans.

Case description

A female dog, German Shepherd inbred, eight years old and 16 kg in weight, from a private pound in the vicinity of Messina, spontaneously died and was sent to the Unit of Veterinary Pathology for necropsy.

At gross examination all organs were evaluated; in particular, the liver, lung, pancreas and prescapular lymph node were sampled, fixed in 10% neutral buffered formalin solution and routinely processed for paraffin embedding. Histological sections (4 µm thick) were stained with haematoxylin-eosin and observed under a light microscope; PAS and Alcian Blue histochemistry were performed on serial sections of liver. Immunohistochemical

doi: 10.17221/8182-VETMED

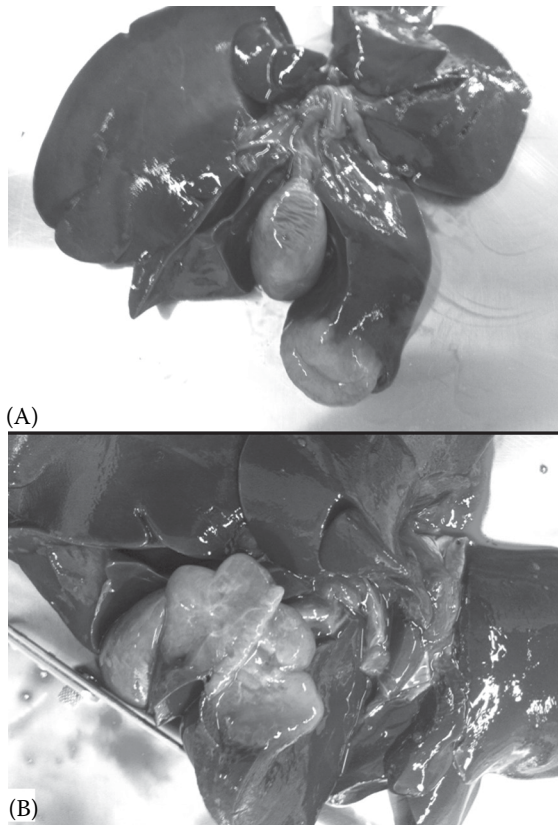


Figure 1. (A) Macroscopically the tumour had well defined limits and was white-grey in colour; (B) the cut surface was homogeneous, with central pseudocystic areas

stainings were applied to liver histological sections, to better identify tissue changes and to differentiate them from other similar pathological features with possible congenital aetiology (Teoh et al. 2006).

Immunohistochemistry was carried out using the following monoclonal antibodies, commercially available from DAKO Cytomation (Copenhagen, Denmark): wide spectrum cytokeratin (AE1-AE3), cytokeratin 7-8-18, 19, 20, CEA and MIB-1. The antibody working dilutions used varied, according to the producer, from 1:200 to 1:400. To avoid non-specific adhesion of serum proteins, histological sections obtained using a microtome were pre-treated with 3% hydrogen peroxide to block endogenous peroxidases in rabbit non-immune normal serum. After application of each primary antibody, for 16 h at 4 °C, a secondary antibody and peroxidase-antiperoxidase complexes were used. The site of immune reaction was revealed using 3-3' diaminobenzidine tetrahydrochlorure as a chromogen, which marked positivity with a brownish stain. Nuclear contrast was obtained with Mayer's haemalum.

At necropsy, the liver showed a moderate increase in volume as well as the presence on the ventral surface of a round greyish area with unclear limits. At the level of the ventral margin of the median right lobe, a large grey nodular bulge, approximately 5 cm × 3 cm in size, firm in consistency and lardaceous, was detected (Figure 1A and 1B). On cut section, the neoformation showed no capsule and cyst-like features with a clearly evident central cavity, containing a small amount of clear aqueous material. Local lymph nodes were within normal size limits. No macroscopically visible changes were determined in the remaining organs.

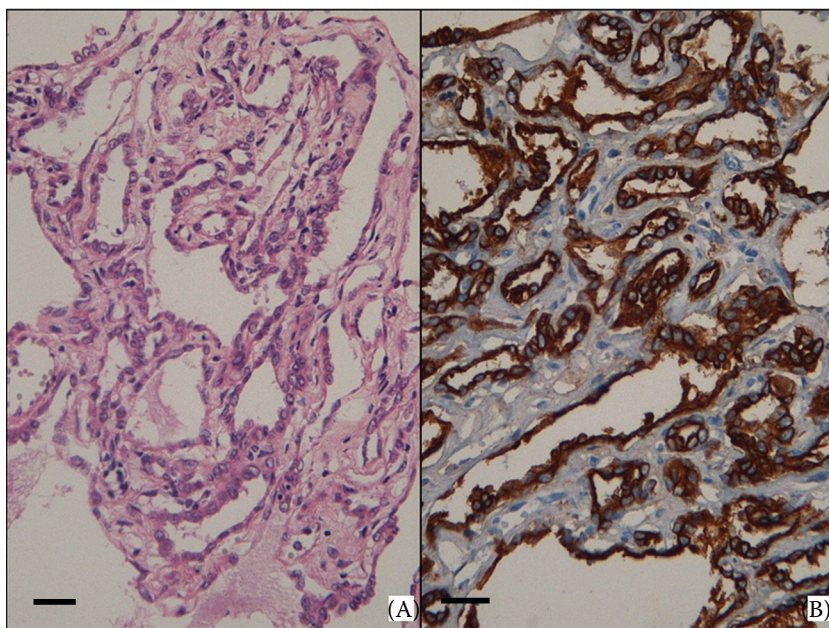


Figure 2. (A) Proliferating cubic cells with oval nuclei and scant cytoplasm; haematoxylin-eosin, bar = 50 µm. (B) Immunocytochemical expression of wide spectrum CK AE1/AE3; bar = 50 µm

Histologically, the liver exhibited well defined sub-serosal cellular proliferation, characterised by epithelioid cells arranged in acinar-like structures lining differently sized lumens. Cystic spaces were optically empty and contained bile increments. A small amount of supporting inter-glandular stroma, comprising scarcely vascularised connective tissue, was seen. Proliferating cells resembled normal biliary epithelium: they were monostratified cuboid or slightly flattened cells, with oval nuclei generally localised in the basal portion and scant cytoplasm (Figure 2A). Sometimes a slight epithelial hyperplasia was seen with no papillary features. Mitoses were found very rarely.

Histochemical staining did not reveal any PAS-positive neutral mucin, whilst Alcian blue PAS pH 2.5 was positive, confirming the lack of congenital biliary cysts. Immunohistochemical examination showed a sharp and diffuse cytoplasmic reactivity of the neoplastic cells with wide spectrum cytokeratins (AE1-AE3) (Figure 2B), and cytokeratins 7-8-18 and 19. Immunoreactions against CEA and CK20 were negative. Growth fraction, evaluated using MIB-1 antibody, was lower than 2%.

DISCUSSION AND CONCLUSIONS

Morphological, histochemical and immunohistochemical features were consistent with a diagnosis of a biliary cystadenoma, a benign neoplasm, which in this case was incidentally discovered in a subject deceased from different causes. This tumour was microscopically characterised by a homogeneous structural arrangement, with monomorphic cuboid elements, without atypia and nuclear pleomorphism. Thus, a well differentiated hepatic cellular growth with a low proliferation index, and not invading blood vessels, was described. The low proliferative activity of the adenomatous cells was demonstrated by the low growth fraction, identified by MIB-1 antibody, which was immuno-reactive in the nucleus of less than 2% of the cell population. Immunocytochemical profiling of keratins, in both aspects of immuno-reactivity and negativity, strongly supported a biliary epithelium histogenesis, typical of a cystadenoma rather than a colangiocarcinoma.

In the available literature on comparative pathology, cholangiomas in humans, with a dense mesenchymal cell stroma, and with normal muscle fibres and oval cells that surround epithelium (Wheeler

and Edmondson 1985; Koroglu et al. 2006), were described.

Intra-hepatic biliary cystadenomas are rare benign tumours of the liver, derived from the intra-hepatic bile duct, and are symptomatic when they cause obstruction of the same ducts.

This benign neoplasm is more frequently reported in cats, whereas it appears to be rarely described in other carnivores, mainly in adults (Marcato 2002). It is characteristically localised in a single hepatic lobe, with an evident polycystic aspect. Ultrasound examination in such cases reveals a cluster of merged, differently sized, round, anechoic or finely granular cysts. Differential diagnosis should consider isolated cysts and polycystic syndrome of the Persian cat: a simple cyst is unique and lacks the typical tendency to merge in groups and the lobar extension, whereas in polycystic syndrome the kidneys are also involved. The hepatic localisation in polycystic syndrome may show clusters of cysts (the tendency of cysts to merge can generally lead to a diagnosis of cholangioma), although the breed and the simultaneous localisation at kidneys make a differential diagnosis possible.

There are different theories on the origin of neoplasms in comparative pathology: today the association between liver carcinogenesis and B hepatitis virus, chronic hepatic disorders (cirrhosis), presence of toxins in food (aphlatoxins), intake of some alkylating antineoplastic agents and trematode infestations is widely known.

In dog, toxicological trials have been carried out to determine the potential carcinogenicity of nitrosamins, but a definite aetiopathogenetic factor has not yet been identified. Moreover, only a very low percentage of patients with hepatocellular carcinoma show cirrhosis. Thus, chronic hepatic diseases seem to play no role in the carcinogenesis of hepatic tumours. Moreover, hepatitis virus has never been isolated from the liver of dogs with carcinoma (Tennant et al. 2004).

According to the current literature (Moon et al. 2011), a dog cholangioma, in the absence of stroma, could phylogenetically evolve towards possible malignant forms. This is in contrast to the situation in humans, where stroma is evident and cases of malignant behaviour are very rare.

In the present case, unfortunately, because of the lack of anamnestic details provided by the owner, we could not follow the evolution of the tumour and consider possible treatments.

doi: 10.17221/8182-VETMED

Acknowledgements

The authors are grateful to Prof. Eugenio Cianflone (University of Messina, Messina, Italy) for the English language editing and proofreading of this paper.

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Received: 2014–10–30

Accepted after corrections: 2015–04–09

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