Diagnostic Exercise

From The Davis-Thompson Foundation*

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Answer Sheet

Title: Dog, liver, cholangiocellular carcinoma.

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Figure 1

Diagnosis: Liver, cholangiocellular carcinoma
Typical gross findings: Cholangiocellular carcinomas may be massive or multinodular. The latter is more common and is characterized by multiple white to tan nodules scattered throughout the parenchyma. The massive form is rarely restricted to one hepatic lobe. The center of the nodules or masses is frequently necrotic, giving them an “umbilicated” appearance. Cholangiocellular carcinomas are highly metastatic and spread frequently to the lungs, lymph nodes and peritoneal cavity. They may also metastasize within the liver. The texture of cholangiocellular carcinomas generally helps differentiating them from hepatocellular carcinomas during necropsy: the latter are soft and occasionally friable while cholangiocellular carcinomas are firm. This dog had an atypical gross presentation for a cholangiocellular carcinoma: many nodules seen within the liver were yellow to dark red due to extensive necrosis and/or hemorrhage within the tumor. The remaining liver parenchyma was altered as well: it varied from yellow to orange and had several friable areas on cut surface that corresponded to necrotic foci on histological examination. Based on gross examination, differential diagnoses included hemangiosarcoma (due to the red color of several nodules) and hepatocellular carcinoma (due to the fact that some nodules resembled normal hepatic parenchyma and that this dog had only rare metastases on gross exam).

Figure 2

Typical microscopic findings: Cholangiocellular carcinomas are composed of proliferated biliary epithelial cells. The cells are often cuboidal to columnar, with round nuclei and moderate...
amount of pale eosinophilic cytoplasm. The cells are generally arranged in structures that resemble bile ducts, consisting of tubules with a lumen. Papillary structures may also be present. Less differentiated tumors may present more solid areas, with rare tubular arrangement. The amount of fibrovascular stroma within the tumor is variable. Vascular invasion by tumor cells and necrosis within the neoplasm are frequent features. The hepatic parenchyma surrounding the tumor may be necrotic or fibrotic. In this case, extensive necrotic areas were observed within the tumor and the remaining hepatic parenchyma. These necrotic areas were peracute (characterized by coagulation necrosis without prominent inflammation) or acute (characterized by coagulation necrosis with massive infiltration of neutrophils) and were accompanied by severe hemorrhage. This influenced the gross appearance of the liver: the majority of the necrotic foci corresponded to the yellow and orange areas. When hemorrhage accompanied the necrosis, these areas were dark red. Another important histological feature was invasion of several lymphatic and blood vessels by the tumor cells. The pancreas had neoplastic cells within blood vessels as well, which was probably the cause of the hemorrhages seen grossly. The two small nodules observed within the lung at necropsy corresponded to metastases. Additionally, multiple organs had intravascular fibrin thrombi within small blood vessels.

Figure 3
**Clinical presentation:** The massive infiltration of the liver by tumor cells and the previous three-week history of anorexia, vomiting and seizures suggest that this dog developed chronic liver failure, which is commonly associated with cholangiocellular carcinoma. This is generally accompanied by elevated serum hepatic enzymes, such as alanine aminotransferase and alkaline phosphatase. Another classic clinical presentation seen in this dog and in other animals with chronic liver failure are neurological signs due to hepatic encephalopathy. The pathogenesis of this condition involves high levels of ammonia in the blood stream due to liver failure. Ammonia is toxic to the central nervous system, causing the appearance of neurological clinical signs.

**Discussion:**
Cholangiocellular carcinoma is a malignant tumor that originates from the bile duct epithelium. It is considered uncommon in dogs, and generally less common than hepatocellular carcinomas. Interestingly, cholangiocellular carcinomas have a relatively high prevalence in dogs submitted to necropsy at our laboratory, being more common than hepatocellular carcinomas and corresponding to approximately 5% of all neoplasms leading to death or euthanasia of the submitted dogs. In a previous study concerning primary hepatic malignant tumors in dogs from our lab, 36/51 tumors were cholangiocellular carcinomas and only 9/51 were hepatocellular carcinomas. The cause of this atypically high prevalence of cholangiocellular carcinomas in our region remains unknown. No breed, sex or age predispositions have been noted. Another interesting aspect is that this high prevalence has been observed since our laboratory opened in 1964.

A study conducted in South Africa shows a similar prevalence of these tumors in dogs; however, no etiology was determined. In humans, many cholangiocellular carcinomas have been linked to infection with *Clonorchis sinensis*, a biliary ductal parasite. Two articles have reported cholangiocellular carcinomas in dogs and cats associated with this same parasite; however, the relationship of the parasite infection and the tumor development remains unknown in dogs and cats. *Platynosomum fastosum*, a feline liver fluke that is similar to *C. sinensis*, is considered common in cats in Northwestern Brazil. Nonetheless, neither of these parasites, which are considered rare in Southern Brazil, have been diagnosed in our laboratory. In humans, hepatocellular neoplasia is frequently associated with chronic liver disease caused by virus, alcohol or metabolic defects. In these cases, the tumor-free liver parenchyma is affected by chronic inflammation and fibrosis. Dogs with cholangiocellular carcinomas generally do not present chronic hepatitis or cirrhosis affecting the remaining parenchyma. Therefore, chronic hepatic inflammation is not considered premalignant in this species as it is in humans.

Histologically, cholangiocellular carcinomas may be difficult to distinguish from metastatic adenocarcinomas, such as those arising in the mammary gland or pancreas. In this dog, a complete necropsy allowed us to confirm the hepatic origin of the tumor. Additionally, some hepatocellular carcinomas may present areas that resemble tubular formation (pseudoglandular pattern), making it difficult to differentiate these tumors from cholangiocellular carcinomas. Rarely, hepatic tumors may also be mixed hepatocellular and cholangiocellular carcinomas. Immunohistochemistry may be helpful in these cases. Cytokeratin 7 is generally used to label cholangiocellular carcinomas, while Hepatocyte Paraffin 1 (HepPar-1) is used as a marker for...
hepatocytes and is therefore used to label hepatocellular carcinomas. Some other tumors, particularly intestinal carcinomas, also may express HepPar-1 in humans and dogs.

Cholangiocellular carcinomas are highly aggressive tumors, mainly because they often affect all liver lobes and because they frequently metastasize. Dogs with this kind of neoplasia may develop clinical signs related to chronic liver failure, tumor rupture and/or metastases to various organs. The clinical signs and death of this dog were attributed to the following mechanisms: (1) chronic liver failure, which led to jaundice and neurologic signs; (2) tumor rupture, which caused severe abdominal hemorrhage; and (3) extensive areas of hepatic necrosis, which might have led to disseminated intravascular coagulation.

References:


*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation. These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the CL Davis website (http://www.cldavis.org/diagnostic_exercises.html).

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